THE EVOLUTION OF GENETIC SYSTEMS

by

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PREFACE

In the present sketch I have attempted to show genetics as the study of systems of heredity and variation, systems which rest on a basis of the chromosomes and are related to one another by processes of natural selection. I believe that the combination of the material basis with the evolutionary framework provides the only means of making sense of biology as a whole. I hope moreover that this elementary exposition will enable its readers to realise that the chromosome theory is now something more than a profession of faith, or even an instrument of genetic discovery; it is the key with which we are opening the door between the physical and the biological sciences.

C. D. D.

December 1938

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...There are three great discoveries which have enabled our knowledge of the interconnection of natural processes to advance by leaps and bounds: first, the discovery of the cell as the unit from whose multiplication and differentiation the whole plant and animal body develops.....Second, the transformation of energy, which has demonstrated that all the so-called forces operative in the first instance in inorganic nature...are different forms of manifestation of universal motion....Finally, the proof which Darwin first developed in connected form, that the stock of organic products of nature surrounding us to-day, including mankind, is the result of a long process of evolution from a few original unicellular germs, and that these again have arisen from protoplasm or albumen which came into existence by chemical means.

ENGELS, *Ludwig Feuerbach*, 1888

CHAPTER I

PREMISES OF GENETICS

LIVING organisms as we know them are things derived by breaking off or reproduction from their like and usually capable of giving rise to their like for an indefinite time. This is the genetic way of defining life. The degree to which organisms arising in this way are like their parents is said to be due to *heredity*. The degree to which they are different is said to be due to *variation* in this heredity.

One proviso must be added to this definition: that conditions outside the organisms be not changed. In nature the differences between organisms depend on differences outside as well as inside them. Smaller size may be due to bad heredity or bad food. We therefore separate these two factors as *Genotype* and *Environment*. Genetics rests on the axiom that the character of an organism depends on the reaction of its genotype and its environment. Where a plant is propagated by grafting or cuttings all over the world and for a great space of time, its environment and its observable characters change continually but its genotype remains the same. When it is brought back to the old conditions its old character reappears. We therefore say that there must be material particles within the organism which reproduce themselves without change and determine this constancy within it. That at least was the simplest assumption and one that was made long before any such particles were seen. The *corpora genitalia* of the ancients became the ids of Weismann and the genes of Johannsen. Now, however, we find that all cells contain certain visible particles lying inside the cell nucleus. These particles alone are indispensable to the reproduction of a cell or of a whole organism. They are characteristic and similar in their behaviour in plants and animals. We therefore assume that the nuclear particles are responsible for heredity. The nucleus is in fact the seat of the genotype very much as the brain is the seat of the mind. We merely know more about the organisation of the nucleus than of the brain.

This brings a contradiction into the notion of genotype and environment. The organ of the genotype is not one but many nuclei distributed throughout the body. These nuclei are surrounded by a material, the cytoplasm, through which they exert their effect on the organism and on one another. They must be capable of interacting in the course of development. The cytoplasm is therefore the agent through which differentiation is established between the parts of the organism. It constitutes an inner environment coming between the organs of the genotype and the outer environment. On these properties depend the adaptations of genetic systems to the great variety of conditions of development we are going to consider in various organisms.

Thus environment is by no means so simple a notion in effect as it might seem to be. The environment for particular purposes depends on whether we are speaking of the whole or of a part of an organism, or indeed of the whole or a part of a species. It may depend also on the stage of development and the relations of parent and offspring. And lastly, by a paradox, it depends on the genotype from which we thought to have separated it. For when we change the genotype we throw the organism into a new environment. A dwarf bean does not meet the same world as a scarlet runner.

Before we go any further let us recall the three vital experiments on which these principles are founded. The first is the proof by Johannsen that the genotype is independent of the environment. Johannsen took a stock of beans (*Phaseolus vulgaris*) descended by self-fertilisation for several generations from one plant. This he described as a *pure line*. He found the seeds produced differed in weight, but that plants grown from the heavier produced seeds no heavier than those from the lighter seed. This was repeated for several generations, but selection continued to have no effect. The new sub-lines within the old pure line had all the same seed weight. Why? Because the genotypes of all the plants in the pure line were the same and the differences between them were due merely to differences in the environment. These effects were not inherited. The environment is therefore powerless to produce a change in a group of organisms without selection; selection is powerless to produce a change without variation amongst the genotypes. And variation is not inherent in heredity in the sense in which Darwin imagined it to be. When, on the other hand, a population containing many different pure lines is selected, it is changed as a whole, because the differences between its constituent lines are genotypic.

The second experiment (although earlier in date) is the proof by Mendel that the genotype is composed of indivisible parts. Mendel crossed members of two pure lines of peas (*Pisum sativum*) which differed in one recognisable respect: one was tall, the other dwarf. The first generation, or F_1, progeny were all tall, but when they were self-pollinated they produced second generation, or F_2, progeny three-quarters of which were tall and one-quarter dwarf. The dwarf all bred true, and so did one of the three quarters that were tall. The rest of the tall plants again gave a three to one proportion of tall and dwarf. Further, when any of these impure talls were crossed with dwarfs (for all dwarfs were evidently pure) half the offspring were tall and half dwarf. Mendel drew a conclusion which is now obvious though it was repugnant to the then prevailing thought; he assumed that the first cross was hybrid for a factor determining tallness, the genotype of each plant having both the factor for tallness (T) and an alternative factor for dwarfness (t) which were inherited from its two parents, TT and tt; and further, that these factors separated in the formation of the germ cells so that some had one and some the other in equal numbers. Hence the hybrid Tt gives germ cells T and t and progeny recombining T and t at random as a result of random fertilisation, in the proportions $1\,TT : 2\,Tt : 1\,tt$. Since Tt shows the undiminished tall character, three of this dominant character appear to every one of the recessive.

From this experiment it follows that the product of fertilisation is genetically double, that its genotype is determined by certain particles or arrangements of particles which retain their individuality from one generation to another, and that corresponding particles from opposite parents separate when the germ cells are formed so that they are genetically single. These particles, which we need not define more accurately for the moment, are now known as *genes*. Mendel's observations of their effect enable us to define a hybrid as a zygote derived from the fusion of dissimilar gametes. They enable us to predict likewise that such a hybrid will itself give rise by *segregation* to dissimilar gametes.

From this experiment followed a whole series of others calculated to discover what happens when an organism is hybrid for several of these gene differences. Usually any particular pair will *recombine* freely, each of the classes for one factor (*A*)—pure dominant, hybrid and pure recessive—consisting of the same proportions (1 : 2 : 1) of the three classes for the other (*B*). Thus a double hybrid *AaBb* gives:

1 *AABB* : 2 *AaBB* : 1 *aaBB*
: 2 *AABb* : 4 *AaBb* : 2 *aaBb*
: 1 *AAbb* : 2 *Aabb* : 1 *aabb*.

Or, taking the externally distinguishable classes:

1 *AABB* : 2 *AaBB* : 2 *AABb* : 4 *AaBb*
1 *AAbb* : 2 *Aabb*
1 *aaBB* : 2 *aaBb*
1 *aabb*,

i.e. 9 : 3 : 3 : 1.

By this experiment Mendel established the free segregation of two factors or genes controlling height and colour. But free segregation meets with exceptions. Where, for example, the cross has been made between *AABB* and *aabb*, more of the *AB* and *ab* classes of gametes may be formed by the hybrid than the alternative, or *crossover*, classes *Ab* and *aB*. Evidently there is some restriction on this crossing-over or recombination. Moreover, the restriction is found to be of different degrees between different pairs of genes. Some pairs have crossed over in 30 per cent. of gametes and others in only 1 or 2 per cent.

When hundreds of pairs of genes have been tested for crossing-over in various species of *Drosophila*, *Zea Mays*, *Pisum sativum* and *Pharbitis*, it has been found that those pairs which show a mutual restriction of crossing-over, or linkage as we say, can be arranged in groups, and that within each group the series of genes is a linear one such that, knowing the proportion of crossing-over between *A* and *B* and between *B* and *C*, we can calculate the proportion between *A* and *C* as a little less than the sum of these two. Finally, the number of these groups is found to agree with the number of separate bodies or chromosomes in the nuclei of the germ cells in the particular plant or animal, 10 in *Zea Mays*, 4 in *Drosophila melanogaster* and so on.

An equally fundamental experiment was carried out by Mendel on fertilisation. He counted the number of pollen grains placed on the style of *Mirabilis jalapa* and proved that one pollen grain was enough to fertilise one seed. Ten years later the essential process was seen by Oscar Hertwig. He watched a sperm entering an echinoderm egg, and saw the fusion of their two nuclei. He had discovered the nature of fertilisation.

These discoveries have translated genetics from undefined assumptions of vitalistic forces and indeterminate influences to defined assumptions of determinate materials. They have given the heredity of living things the same atomic character that was already implied by their chemical structure. The observations of fertilisation and meiosis enabled Weismann to distinguish between the materials carried in the cell nucleus and passed down from generation to generation as the *germ-plasm*, and their temporary product in each generation as the *soma*. The germ-plasm was, in a sense, responsible for the genotype, the soma for the phenotype. Breeding experiments and cytological observations agreed in contradicting the primitive superstition that heredity was a direct relationship between parent and offspring. They showed that the relationship was not between their appearances but between their hereditary materials. Our next task is therefore to see what these materials are and how they are handed down from generation to generation.

Since the contributions of the mating nuclei are equivalent, the results of reciprocal crosses between varieties and species are similar. Exceptions to this rule are rare. Differences are found which are inherited on the female side only, showing that the cytoplasm is carrying specific self-propagating elements like those in the nucleus. We can however attempt to define the part they may play only when we understand the more precise action of the visible determinants in the nucleus. When we have done this we shall return to the cytoplasm.

CHAPTER II

THE SUBSTANCE OF HEREDITY

As a single cell grows into a mature organism it divides into many cells and its nucleus into many nuclei. It is then that we are able to understand the particulate character of its permanent or heredity-making structures. We recognise nuclei by their having a characteristic method of division, *mitosis*, which provides for the products of division being genetically identical.

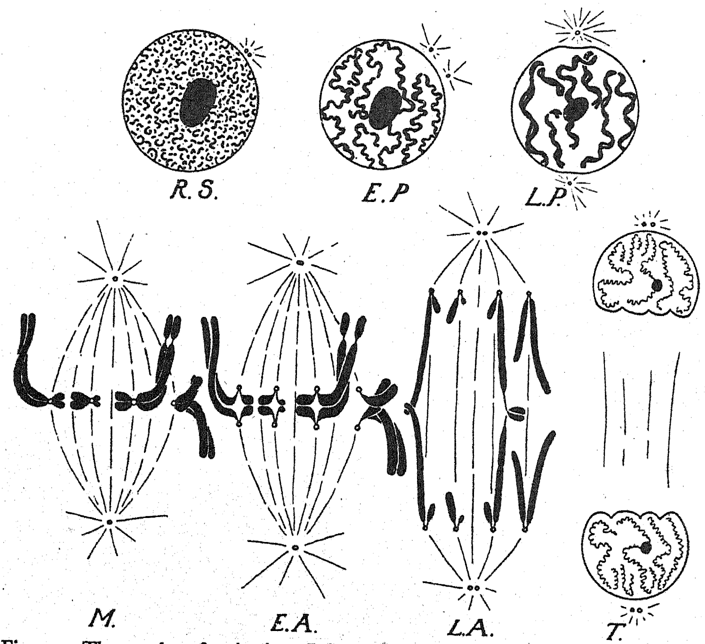

Fig. 1. The cycle of mitosis. *R.S.* Resting stage with large nucleolus. *E.P.* Early prophase with double chromosomes in relic spirals. *L.P.* Late prophase with centrosomes at opposite sides of nucleus. *M.* Metaphase with four chromosomes orientated on plate of spindle. *E.A.* Early anaphase with centromeres divided. *L.A.* Late anaphase. *T.* Telophase with nucleolus being re-formed at the secondary constriction. (Darlington, 1937 *a.*)

The resting nucleus is globular and bounded by an even surface. The nucleus is sometimes optically homogeneous in life but differential refractivity as well as certain fixations can be made to reveal its structure. It consists of a compactly coiled mass of threads, the chromosomes. The first sign of mitosis is that these threads become separated from a watery substrate or sap. They are then seen to be loosely coiled and lying in closely associated pairs, or as we may say each chromosome is double. They then begin to shorten and thicken to form double cylinders or rods (Fig. 1). They all show one, or perhaps more, constrictions at constant points in their length.

This *prophase* is ended by the boundary or interface of the nucleus breaking down and its space being invaded by the less watery particles of the cytoplasm which have previously been kept out. These invading particles form a spindle-shaped mass around the chromosomes. This mass contains even less water than the surrounding cytoplasm. The chromosomes come to lie in a plane across the middle of this spindle and they are seen to lie regularly with one constriction on the equator of the spindle, although the rest of the chromosome, its body, may lie off the equator or even in the cytoplasm. The constriction is seen, with suitable treatment, to be occupied by a small body, the *centromere* or mechanical centre of the chromosome, which, unlike the rest of the chromosome, has not yet divided. This stage, with the chromosomes forming a plate half-way between the ends or poles of the spindle is *metaphase* (Fig. 2).

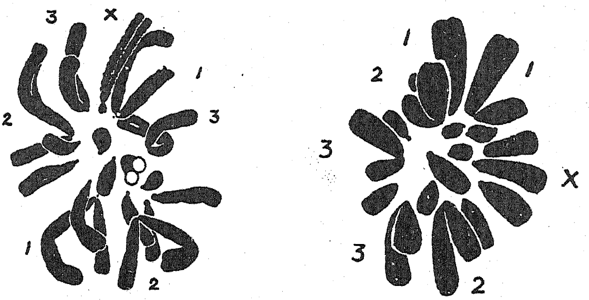

Fig. 2. Metaphase of mitosis in early and late spermatogonia of *Chorthippus* (Orthoptera) showing 3 pairs of chromosomes with median centromeres, 5 pairs with subterminal centromeres and the single sex chromosome (*X*).

After a short period the stability of the situation is changed by the simultaneous division of the centromeres of all the chromosomes. Each centromere splits into halves, which move apart from one another towards the opposite poles, pulling their chromatids or half-chromosomes after them. Between the two groups the spindle stretches, pushing them farther apart This stage of separation is *anaphase.* When the sets of chromatids come near the poles, two new nuclei are built up again. This last stage is *telophase.*

While the nuclei are returning to their resting condition a fine spiral appears inside each chromosome, and its coils slightly loosen and becoming closely entangled disappear in the optically homogeneous nucleus. The nuclear cycle is complete. If, however, we compare this last view with the first we see that the coils which gradually become fewer and straighten out during the contraction of prophase are a direct continuation of those seen at telophase. They are *relic coils.* And while they are disappearing at prophase we must suppose that a new spiral is developing inside each chromatid for the new mitosis.

It is by developing an *internal* coil that the chromosomes contract lengthwise and become conveniently mobile during mitosis. When the coiling fails (exceptionally in certain Protozoa, and abnormally in higher organisms) the chromosomes remain long, so long that the daughter chromatids may fail to separate at anaphase, and a single nucleus is restored with a double number of chromosomes. Such under-coiled chromosomes have more coils than the normal but they are of smaller diameter, so it is clear that the whole nuclear cycle consists in a process of diminishing the number and increasing the diameter of coils in a chromosome. During prophase two successive coiling cycles overlap.

Although the separation of chromatids takes place at anaphase it will be seen that the division of the chromosome into two chromatids is accomplished during the previous resting stage, when the threads are dispersed in the nucleus and half uncoiled. How this division must be supposed to work is a molecular problem. It depends on the molecular structure we assume in the chromosome. It seems likely that the chromosome is a permanent carbon-nitrogen chain with long active side chains at intervals. Division would then consist in the attraction and laying down of identical component particles next to the original thread and these particles would fuse to make a new thread.

It is an essential property of these essential materials of life that the attraction on which the division of the chromosomes depends is between identical elements and is limited to pairs. Owing to this specificity of attraction, each chromosome divides into two exactly equivalent daughter chromatids, and the two daughter nuclei are also exactly equivalent in chromosome content; they contain the same number of chromosomes of the same sizes and shapes and composed of the same linear arrangements of particles. Hence so long as mitosis regularly continues every nucleus formed has a constant outfit of chromosomes. This constancy applies to the whole of an individual. It ensures the permanence of the genotype, and within limits the constancy of the species.

CHAPTER III

SEXUAL REPRODUCTION

SOME of the Protozoa and Algae so far as we know undergo no other kind of nuclear division than mitosis. Their reproduction is asexual or vegetative. Nearly all the higher organisms, on the other hand, have a special method of reproduction involving two compensating changes in the nucleus—*fertilisation* and *meiosis* or reduction. The combination of these two processes is known as sexual reproduction. Fertilisation consists in the union of the nuclei of two gametes in forming a zygote. In view of the self-propagating permanence of the chromosomes the zygote has two sets of the chromosomes of which each gamete has one. And in so far as the gametes are from related parents the two sets are related and therefore correspond in form and structure, so that each type of chromosome is represented in the zygote by two homologues. The zygote is therefore said to be *diploid* (with $2n$ chromosomes) and the gamete *haploid* (with n chromosomes).

Meiosis consists in two divisions of the diploid nucleus of the mother cell accompanied by one division of its chromosomes. Each chromosome pairs with its homologue, so that $2n$ chromosomes form n pairs during the first division and the chromosomes of each pair pass to opposite poles without separation of their chromatids. These chromatids then separate at the second division. Each of the four nuclei therefore have one of the four chromatids of each pair of chromosomes. They are haploid nuclei once more, but with the chromosomes in different combinations in different cells. Thus a hybrid with four chromosome pairs *Aa*, *Bb*, *Cc*, *Dd* will give gametes *ABCD*, *ABCd*, *aBcd*, and so on.

In most of the lower organisms the fusion of the gametes is followed immediately by the compensating meiosis. The diploid phase merely lasts through one resting stage. In the higher organisms the diploid phase is the main part of the cycle and the haploid is reduced to one resting stage in the higher animals. In man the diploid phase consists of about 50 mitoses in sequence yielding some 10^{14} cells.[1] The prolongation of the diploid stage is achieved in the Basidiomycetes by a special device. The two gamete nuclei divide side by side in every cell of the plant. As soon as they fuse, meiosis takes place. Until then we have a diploid organism with only haploid nuclei.

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[1] White, 1937.

The two important factors in permitting sexual reproduction are usually the bringing together of the two gametes from different places and the providing of a food supply for the new diploid individual. These conditions are usually satisfied by *sexual differentiation*, that is by a division of labour between the two gametes. One travels with the minimum burden, the other merely waits with the food supply. The one is the male cell or spermatozoon, the other the female cell or egg. When the same parent individual bears both it is said to be hermaphrodite. When separate individuals bear opposite sex cells the individuals themselves are said to be male and female and the species as a whole is said to be sexually differentiated.

Sexual differentiation of gametes begins with a minimum where there is no difference in size between the gametes, only in movement, as in *Actinophrys* or *Spirogyra*. It ends with the extreme of difference in size between a sperm and a bird's egg, which is many million times larger.

Sexual differentiation of individuals bearing the gametes may apply to the haploid individuals where a haploid generation is retained, as in Protista and Bryophyta. In the higher organisms where the haploid generation is telescoped, the sex of the gametes is determined by the differentiation of the preceding diploid generation. The haploid generation bears, not a sexual character of its own, but that which has been imprinted on it by the parent male, female or hermaphrodite of whose body it forms a part. In the Bryophyta where the haploid plants lead an independent life their sex is an individual property directly determined.

CHAPTER IV

MEIOSIS: PAIRING AND CROSSING-OVER

THE first question about meiosis is of course what makes it different from an ordinary mitosis. The character of the division is undecided at the preceding telophase. This is shown by one of the products of mitosis in certain fungi undergoing meiosis and forming an ascus while the other undergoes mitosis, e.g. in *Peziza*.[1] It is also shown by the nature of the division, mitosis or meiosis, being determinable experimentally during the preceding resting stage in certain diatoms.[2] The difference has arisen before the beginning of prophase, however. In mitosis the chromosomes divide, as we saw, during the resting stage. In meiosis they begin the prophase still undivided. The difference must be established during the resting stage.

We know from the evidence of X-ray changes that the division is actually at a variable time in the different intermitotic resting stages, depending perhaps on their duration.[3] The resting stage of the mother cell which is to undergo meiosis can be extremely short. But, whether it is long or short, prophase always begins too soon for the chromosomes to have divided.

We saw that in mitosis the particles of each chromosome attract similar ones to themselves during the resting stage, so that one thread reproduces or becomes two. This reproduction is described as division and is followed by the association throughout prophase of the two chromatids which arise from the division. At the beginning of meiosis, on the other hand, the chromosomes appear as single threads and the separate homologues therefore attract one another. In the diploid, unless it is a hybrid, there are two homologues of each kind of chromosome corresponding in all their parts. These chromosomes come to lie side by side in pairs.

The chromosomes at this thin thread stage show a granular structure not usually seen during the rapid early prophase of mitosis. They look like strings of unequal beads unequally strung together. These beads are the *chromomeres*. In homologous chromosomes they correspond in number, size and position, and each chromomere pairs with a similar partner. The centromere stands out from its neighbouring chromomeres, being further separated from them than they are from one another.

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[1] Wilson, 1937. [2] Geitler, 1934. [3] Mather, 1937.

The chromosomes usually begin to pair near their ends, but sometimes near their centromeres. Where the centromere lies near an end the most regular result is attained. This regularity is facilitated in many animals by all the ends which are going to pair first lying close together to one side of the nucleus before pairing actually begins. Once pairing has begun, whether at a centromere or at an end or at both at the same time, it passes along the chromosome like the closing of a zip-fastener.

When pairing is complete the diploid complement of chromosomes is present as the haploid number of *bivalent* chromosomes.

In this way the mitotic position of association of similar threads in pairs is restored. The double thread or *pachytene* stage is in a stable condition, which unlike the mating-thread stage may be indefinitely prolonged. Only one change is observable; the partner chromosomes become coiled round one another, *relationally* as we say to distinguish this coiling from the internal coiling already referred to. Pachytene is ended by four changes which always occur together. The chromosomes each divide into two chromatids; at a few points along each pair chromatids of partner chromosomes cross over by breakage and reunion at corresponding points; the chromosomes separate and cross-shaped arrangements of the chromatids, *chiasmata*, consequently arise at these points; and finally, in doing all this the relational coiling of the chromosomes is largely undone. When these changes are complete we have the *diplotene* stage (Figs. 3*a* and 17).

The detailed mechanics of this remarkable series of changes we shall go into later. For the present we must notice, first, that the division of the chromosomes should lead to their falling apart if attractions are limited to pairs of threads; and secondly, that, since chiasmata involve exchanges of partner between members of two pairs of chromatids, they are bound to hold all four together in spite of this limitation. Thus, while all association of the partner chromosomes is conditioned by attraction, this attraction is between chromatids, not between chromosomes after the beginning of diplotene. Not only this, the partners begin to show mutual repulsion. Where only one chiasma is formed between two chromosomes the four arms open at right angles to form a cross. Where there are two chiasmata the loop between them opens

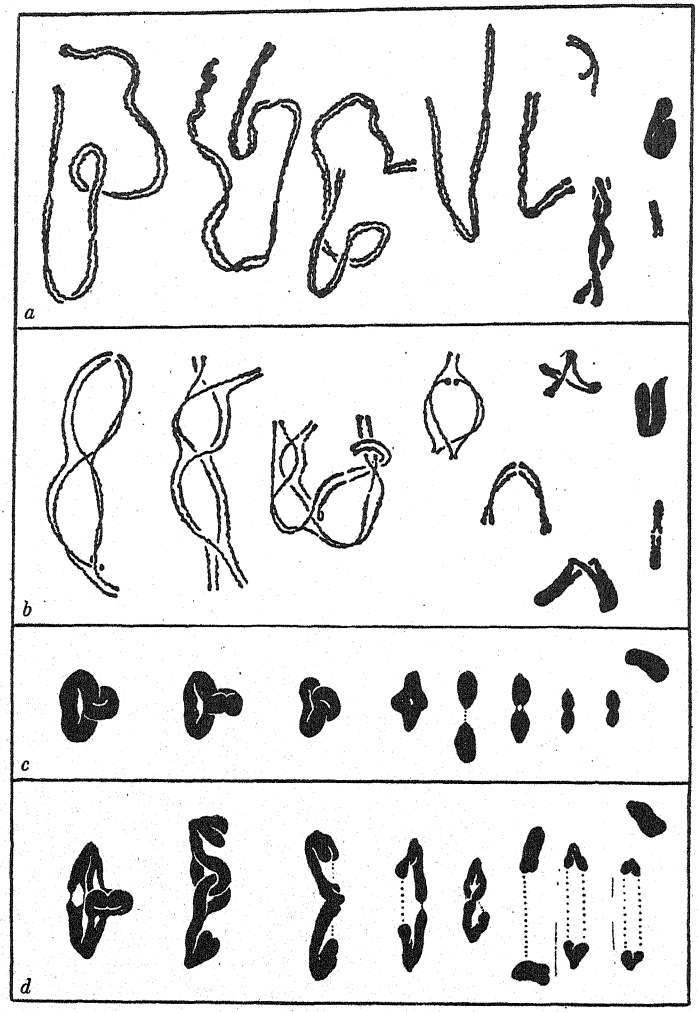

Fig. 3*a*. The first division of meiosis in *Chorthippus*. *a*. Pachytene. *b*. Diplotene; 8 bivalents have one to three chiasmata each while *X* is unpaired. *c*. Metaphase. *d*. Anaphase. Each series is shown as though in a Mercator's projection of the cell, *X* to the right. Centromeres not shown. (After Darlington, 1937 *a*.)

to form a flat circle. What remains of the relational coiling is obliterated.

The chromosomes begin to contract into their internal spiral and the effect of their repulsion now becomes more marked. It shows itself in two ways. In closed loops the repulsion is necessarily stronger than in the open arms of the ends adjoining them, their parts being closer together. These loops expand at the cost of the open arms; the chiasmata slip towards the ends. Secondly, the associations of the two arms containing the centromeres extend at the cost of the two arms not containing them (Fig. 3*a*). In both these cases there is more or less movement of chiasmata towards the ends of the chromosomes. This *terminalisation* occurs in all organisms, in greater or less degree, chiefly according to whether the chromosomes are small or large. Again we have a zip-fastener movement.

There is a third possibility when the centromeres lie near the ends in open arms adjoining a closed loop. When this loop is small the nearest chiasma may perhaps move towards the centromere. In no case of course can a chiasma cross a centromere because the centromere is single. Not only this but the expansion of centric loops shows that there is a specially high repulsion between the centromeres of partners, and their repulsion will increase if the chiasma moves towards them and brings them closer together.

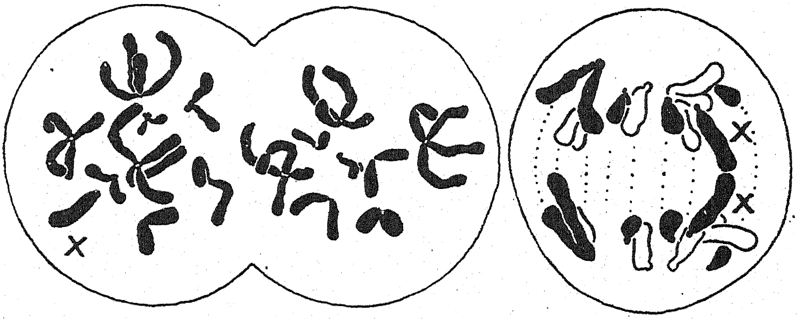

Fig. 3*b*. Left, the two second metaphases in *Chorthippus* with 8 and 9 chromosomes. Right, second anaphase, with *X*.

The extreme of this centric repulsion is found, as we should expect, where the chromosomes are smallest, as in Lepidoptera and most Dicotyledons. All the chiasmata move away from the centromeres to the ends and give terminal chiasmata; and if two are formed between one pair of arms they fuse at the ends, the penultimate association of chromatids replacing the ultimate one at the terminal chiasma.

Thus where the chromosomes are small the bivalents become rods or rings, rods having one terminal chiasma and rings having two. Where, on the other hand, the chromosomes are large the bivalents remain very much the same shape as at diplotene. The chiasmata are separated by more even loops. They are, as we may say, equilibrated and their number remains the same, from one to as many as fifteen but usually two or three. Each pair of chromosomes in any species has a characteristic average frequency of chiasmata under standard conditions.

If the nucleus is small, as in mother cells on the male side, the bivalents become evenly spaced in it, and if they are very short most of them lie on the spherical surface of the nucleus. If the nucleus is large, as in mother cells on the female side, the bivalents are less evenly spaced. The same repulsion which apparently acts between all chromosomes in all prophase nuclei acts also within bivalents, but it is insufficient to secure complete terminalisation in large bivalents. It is also insufficient to secure even spacing in large nuclei. The repulsion is an inverse function of distance. It is, however, insufficient to overcome the powerful attraction of homologous threads in pairs at all stages of prophase.

At the last stage of prophase, *diakinesis*, the chromosomes have come to be contracted a little more than at metaphase of mitosis, they are a tenth their pachytene length in *Lilium*, a fifteenth in *Zea*. They are associated by terminal or interstitial chiasmata in pairs, and the members of these pairs no longer attract but repel one another. Since the chiasmata themselves are the result of crossing-over, such as we have already inferred in breeding experiments, we see that crossing-over is a condition of the pairing of the chromosomes being maintained from pachytene to metaphase. Hence also it is a condition of the reduction of the number of chromosomes and of the regular character of meiosis and sexual reproduction. This principle is true of all sexually reproducing species. It governs, as we shall see later, the character of every genetic unit from the gene to the species. It is the central fact of genetics.

CHAPTER V

MEIOSIS: THE PROCESS OF ASSORTMENT

OUTSIDE the chromosomes meiosis continues to follow the same course as mitosis. The chromosomes themselves, on the other hand, follow a course modified in essential respects by their association in pairs, an association which results from the initial difference between the two types of division.

When the spindle breaks into the prophase nucleus the bivalents first come closer together, and then arrange themselves in a metaphase plate half-way between the two poles. But their internal relationships are very different from those of simple mitotic chromosomes. The two centromeres of each bivalent lying in the spindle are axially co-orientated, that is to say they lie on an arc or axis passing through the two poles of the spindle. One centromere lies on one side of the equatorial plate, its partner a similar distance on the other side. As this is happening they move apart, so that as a rule they are nearly as far from one another as each of them is from the pole on its side. If there is a chiasma close to the centromeres the segments of chromosome between them and this chiasma are drawn out into a finer thread than other segments: they are evidently under tension. The centromeres are repelling one another even more strongly than at diakinesis. Meanwhile, the bivalents adjust themselves laterally, so that seen from the pole they are, as in mitosis, evenly distributed on the plate, while any long free arms of peripheral bivalents lie outside the spindle in the cytoplasm. They remain in this equilibrium position for a short time. Suddenly the attraction between chromatids lapses. The centromeres of partners then move apart and draw their attached chromatids towards the opposite poles (Fig. 4).

The two nuclei that are thus formed at telophase resemble those at a mitotic prophase inasmuch as the bodies of the chromosomes are double, although the centromeres are single. There is, so to speak, the haploid number of chromosomes, but the diploid number of chromatids. They also differ from ordinary telophase nuclei in the rapidity with which the next metaphase follows, and in the absence of any further division of the chromosomes. In some organisms no resting stage intervenes, and at the second metaphase the chromosomes are still super-contracted as at the first division. In others there is a short resting stage, the chromosomes partly uncoil, and at the second division are coiled only as at mitosis.

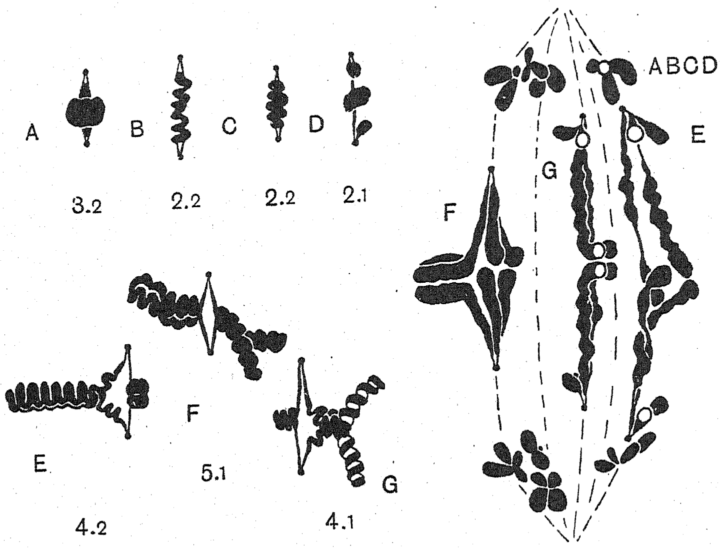

Fig. 4. First metaphase and anaphase in *Uvularia* ($n = 7$), showing how the separation of chromatids distal to the chiasmata in the long chromosomes (*E, F, G*) with more numerous chiasmata delays them relative to *A, B, C* and *D*. The numbers of total and terminal chiasmata are given under each bivalent. The chromatids are internally coiled in pairs at metaphase, separately at anaphase. Centromeres are shown. (After Darlington, 1937 *a*.)

At the beginning of the second metaphase the four arms of each chromosome lie wide apart, joined only by the still undivided centromere, and only just before anaphase do they somewhat irregularly come together, touching perhaps only at the ends or not at all. Anaphase of this division is thus determined simply and directly by the division of the centromeres; contact of the bodies of the chromosomes is superfluous. This process shows what is mechanically essential in mitosis and what is not. The centromere is the sole internal agent in separating the chromosomes at anaphase (Fig. 3*b*).

The first important consequence of these two divisions is the reduction of the chromosome number from the diploid to the haploid, which owing to the segregation of homologues includes a member of each set. But these chromosomes are no longer the unaltered parental chromosomes. They have recombined their parts by crossing-over. Numerically the reduction is due neither to the first nor to the second division of the nucleus, but to the combination of the two with no division of the chromosomes between them. Qualitatively the "reduction" or separation of the corresponding parts of the partner chromosomes occurs at the first division or the second division according to the position of the segment. Obviously the separation of the parental centromeres takes place at the first division. The same applies to the parts between the centromeres and the chiasmata nearest to them. On the far side of the nearest chiasma the second division is

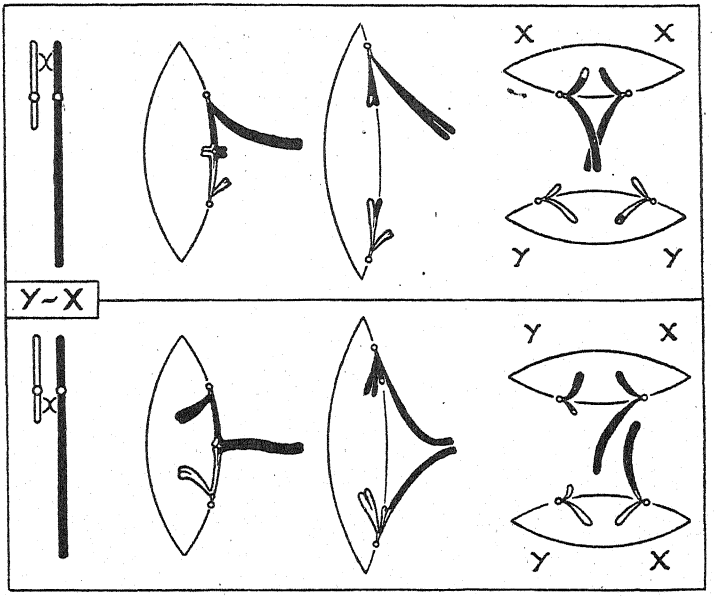

Fig. 5. Meiotic behaviour of a pair of chromosomes, *X* and *Y*, where *Y* has lost a terminal segment present in *X*. Above, crossing-over takes place between the centromeres and the equal ends. Below, crossing-over takes place between the centromeres and the inequality so that the first division is "equational", the second "reductional". Note, all four chromosomes produced at second telophase are different in origin in both cases. Cf. Fig. 17, p. 73.

reductional. Beyond a second chiasma the time of reduction depends on the relationship of the different crossings-over between chromatids at the two chiasmata. The importance of this we shall see when we consider hybrids (Fig. 5).

Meanwhile we must notice that owing to crossing-over, meiosis gives rise to four nuclei all different from one another in regard to the parental origin of every member of its haploid set of chromosomes. Furthermore, owing to the positions of crossing-over differing for each bivalent in different mother cells, no two will give the same kinds of result in the recombination of differences between the parental chromosomes, provided of course that there are enough differences to be recombined. Sexual reproduction is thus a mechanism which secures the greatest possibilities of recombination of genetic differences. This is its one primary and universal function. All others are derived from it.

We must also notice that meiosis occurs in the same way in its mechanical and therefore genetical essentials in all sexually reproducing organisms. It is this cytological uniformity which explains why the principles of heredity, established separately in the reproduction of a few organisms, such as *Pisum* and *Zea Mays*, *Drosophila* and the mouse, confirm one another. And it is this uniformity which assures us that the same principles will equally apply to all sexually reproducing organisms even where, as in men or mules, experimental breeding is inconvenient or impossible.

Finally, we must notice that the invention of meiosis in previously mitotic organisms was the last critical step in the evolution of genetic systems, since it made sexual reproduction possible. Later we shall see from the ways in which it can be reversed how it must originally have come about.

CHAPTER VI

CHANGE OF QUANTITY: POLYPLOIDY

FAILURE of mitosis happens regularly in some animal tissues, and in all plants it may take place under shock. It gives rise to a nucleus with a doubled number of chromosomes. A diploid nucleus ($2x$) will therefore give a tetraploid ($4x$), and hence all its descendants are tetraploid nuclei as constant in number as the diploid. Their cells will under the best conditions be twice as large as corresponding diploid cells and will therefore develop giant tissues and giant organisms. This is generally true of the flowering plants. Organisms however seem to be adapted to a most favourable size, and if this adaptation is inflexible no increase in size but rather a reduction may follow the doubling of the chromosomes; this is true of some mosses and insects.

Doubling, or more properly a failure of reduction, may likewise occur at one of the two divisions of meiosis, especially where pairing of chromosomes has abnormally failed. Instead of haploid gametes or a haploid generation, corresponding diploids appear. When the next fertilisation takes place, diploid and haploid nuclei fusing, a triploid ($3x$) is produced (Fig. 6).

Triploids and tetraploids arise very frequently in nature and in experiment amongst both plants and animals. In animals, however, the general necessity of cross-fertilisation usually prevents an isolated tetraploid from leaving progeny, for it is usually sterile with its diploid relatives and a triploid itself is always infertile. New species do not therefore readily arise from polyploidy in animals, but nearly half the species of flowering plants owe their origin to this change of quantity. Wheat, oats, potatoes, plums and tobacco are polyploid in nature and in cultivation. They have four or six times the *basic number* of chromosomes, x, found in the gametes of their diploid relatives.

The behaviour of polyploids at meiosis is significant in theory and in practice. Take first the *triploid*. It has three chromosomes of each type instead of two as in the diploid. When they pair during prophase only two chromosomes come together at any one point. The third is left out. As in the reproduction of chromosomes, attraction is limited to pairs. In another part of the chromosomes a different one of the three may be left out; they may change partners (Fig. 7). If then chiasmata are formed at different places between one chromosome and both the other two, the trivalent is maintained; all three are held together until metaphase. If, however, one has been left out in the original pairing, or having paired has failed to form chiasmata, it is left unpaired, a univalent, at

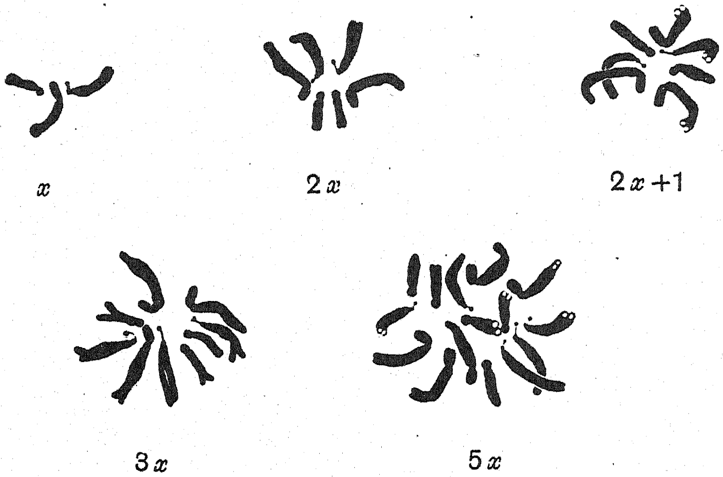

Fig. 6. Complements found in *Crepis capillaris* ($x = 3$). Note the nucleolar constriction separating the small "satellite" of one chromosome. After Navashin, 1926, and Hollingshead, 1930.

metaphase while the other two behave like a normal bivalent. It follows that in all triploids, odd chromosomes are sometimes unpaired. Where 2·5 is the average number of chiasmata formed in each set of three, about a third of these sets are represented at metaphase by bivalents and univalents, two-thirds by trivalents.

Just as no regular result can follow from the association of three chromosomes in pairs during prophase, so there can be no regular co-orientation of the three centromeres of a trivalent at metaphase or regular segregation of its members at anaphase. They come to lie in various ways according to the positions of their chiasmata in relation to their centromeres and the chance of their first moving under the influence of their repulsions on the spindle. These different ways may be classified as linear, convergent or indifferent. The *linear* arrangement (all in a row) is favoured if all three centromeres have chiasmata very close to them so that all three are held near together. The *convergent* arrangement (one repelling two opposite) is favoured where the centromeres are farther apart and equidistant, especially when the chiasmata are terminal. The *indifferent* arrangement with one

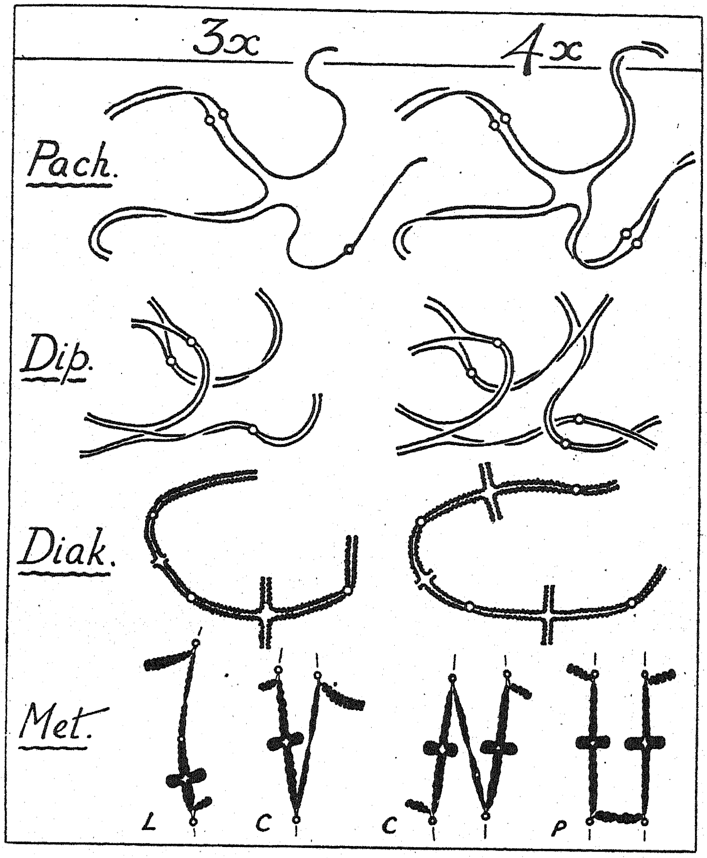

Fig. 7. The first meiotic division in triploids and tetraploids, showing the formation of trivalents and quadrivalents with linear, convergent and parallel co-orientations. The centromeres are represented by rings.

showing no tension with either of the other two arises when this one is remote and the other two close together (Fig. 8).

Where the centromeres lie convergently, two chromosomes will pass to one pole and one to the other. Where they lie linearly or indifferently the equatorial one will be left on the plate and will behave at anaphase as a univalent. Its origin will still be recognisable, if it is large enough and has had an interstitial chiasma, by its chromatids, unlike those of a true univalent, lying wide apart distal to this chiasma.

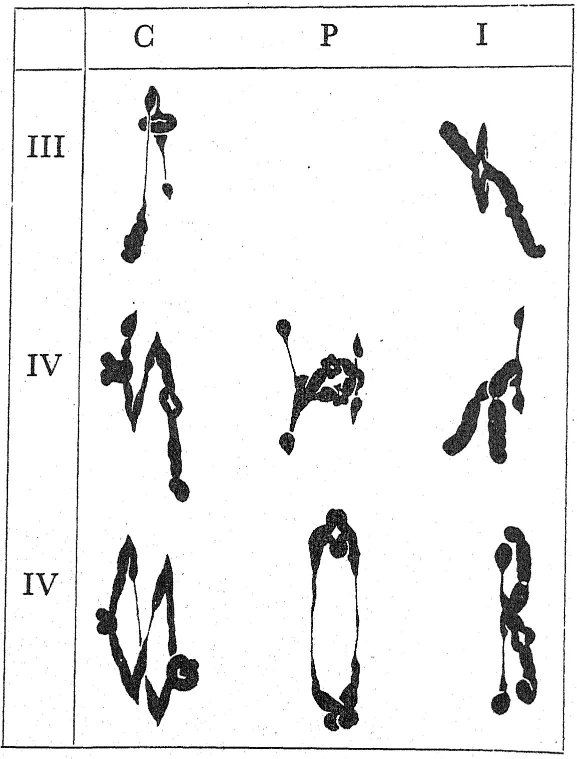

Fig. 8. Forms of trivalent and quadrivalent found in polyploid species of *Tulipa* with convergent, parallel and indifferent co-orientations. (From Upcott, 1939.)

Univalents, true or false, lying on the plate, divide after the bivalents have separated. Anaphase comes too early for them. They divide, as mitotic chromosomes do, by the division of their centromeres. But lagging behind the bivalents in this way they may fail to catch them up and be left outside the daughter nuclei. Indeed true univalents characteristically move on to the plate only at the end of metaphase or beginning of anaphase. They may even remain off the plate, on one side of it. They will then be included in the nucleus formed on that side.

At the second division we therefore have in each nucleus the normal double chromosomes together with some single chromosomes if univalents have successfully divided at the first division. Two chromosomes derived from one trivalent no longer show any connection. The normal chromosomes divide normally. The daughter univalents, unable to divide again, may again lag on the plate and are then often lost in the cytoplasm at telophase.

A triploid therefore gives reduced nuclei containing the haploid set together with a random distribution of the extra set, each chromosome of which has half a chance of getting into one of the four nuclei—or rather less if some are lost. Thus a triploid hyacinth ($3x = 24$) gives pollen grains with all numbers from 8 to 16. Some being lost, however, the modal frequency is 11 and not 12.

The properties of *tetraploids* can be predicted in some detail from those we have noted in triploids. The chromosomes pair two by two at pachytene. They occasionally change partners, and they then recall the shapes of diplotene bivalents. The same mechanical condition (an attraction in pairs) produces the same result at different stages of prophase in diploids and tetraploids. The nature of the homologous threads, chromatids or chromosomes, makes no difference to the attraction.

According to the possibilities afforded by the exchanges of partner and the formation of chiasmata in a limited frequency in different parts of the chromosomes, either one quadrivalent, two bivalents or rarely a trivalent and univalent are formed by any particular group of four chromosomes. Hence as in triploids the associations produced by any particular group are variable. In *Primula sinensis* ($4x = 48$) 12 quadrivalents are frequently formed, but in exceptional tetraploid sperm mother cells of *Culex*, where most chromosomes form only one chiasma, quadrivalents are rare. In a locust, *Schistocerca*, with similar tetraploid cells the longer chromosomes with two, three or four chiasmata form quadrivalents, while the shorter chromosomes with never more than one chiasma do not.

Quadrivalents arrange themselves in linear, convergent or indifferent order like trivalents. But apart from these they may also lie with two pairs of centromeres parallel and, relative to one another, like two indifferent bivalents. Again the linear and indifferent configurations leave lagging "univalents" on the plate while the convergent and parallel ones have a normal and regular segregation. A tetraploid under the ordinary conditions described is therefore incapable of having a regular segregation and forming uniform gametes unless it develops some property which prevents exchanges of partner at pachytene or reduces or stabilises its chiasma frequency. How such properties can arise and enable tetraploids to compete on equal terms with diploids, further considerations will show.

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CHAPTER VII

CHANGE OF POSITION

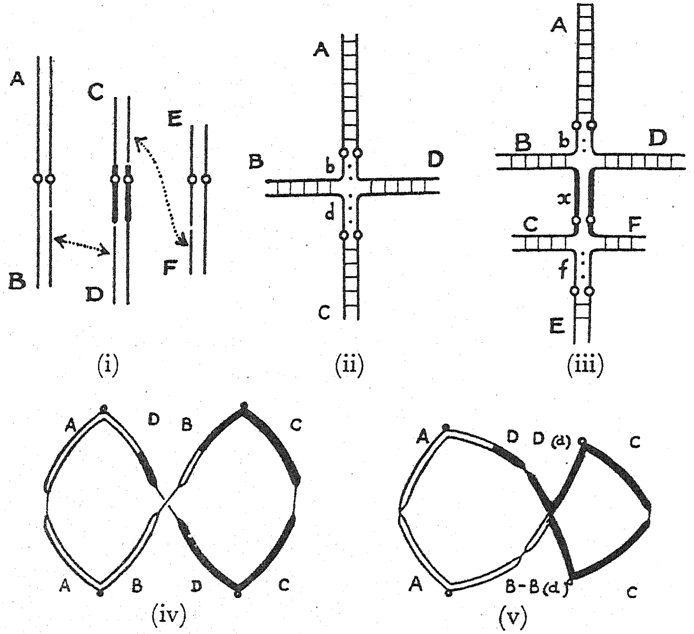
THE chromosomes, as we have seen, are linear arrangements of particles which correspond with the linear arrangements of genes inferred from breeding experiments, and like them are constant and permanent. This is the material basis of heredity. We now have to consider the material basis of variation.

All chromosomes are liable to undergo changes in their potentially permanent or genetic structure. Crossing-over is of course such a change. But it is recurrent and predictable. It recombines what is there already; it produces nothing new beyond this. But the mechanism is significant. Two threads break, and their broken ends rejoin in a new combination.

Structural changes take place exceptionally and sporadically which give rise to new types of chromosomes. And they do so by breakage and reunion as in crossing-over. They differ in one essential, however, from crossing-over, namely that they do not take place during the pachytene stage nor by breakage at corresponding points in homologues. They probably take place for the most part during the resting stage. At this time the chromosomes, except at their free ends, are still under a coiling stress. If one breaks the ends must fly apart and are not likely to rejoin again. If two break, or one breaks at two places, the different ends are therefore more likely to rejoin in a new combination than in the old one. Since these reciprocal changes are particularly frequent both in nature and under X-ray treatment it seems probable that one break is inherently likely to determine another break near it, possibly by the sudden release and movement of the broken ends which (since they are capable of rejoining) must be in an unstable condition for the moment.

A single break without rejoining divides the chromosome into two parts and leads to the loss or *deficiency* of the broken part without a centromere, the *acentric* fragment. A double break and rejoining within a chromosome leads either to *inversion* of the segment between the breaks or its *deletion* from the chromosome, again as an acentric fragment (or ring if its ends join up). Two breaks in different chromosomes, with rejoining, lead to *inter-*

change, which may give two new normally constructed chromosomes or, if the rejoining is the wrong way round, to one *dicentric* chromosome and one acentric chromosome. The two chromosomes concerned may be homologous or not, the breakages and recombinations taking place, it seems, largely according to the chances of position (Fig. 9).



(i) (ii) (iii)

(iv) (v)

Fig. 9. The results of interchange hybridity. (i) Three pairs of chromosomes between which two interchanges occur. (ii) and (iii) The pachytene configurations of four and six chromosomes produced by one and two interchanges: *x*, differential segment; *b*, *d*, and *f*, interstitial segments. (iv) Convergent co-orientation in a ring of four produced by terminalisation of four chiasmata from (ii). (v) Formation of a chiasma in the *d* segment in addition. (After Darlington, 1937 *a*.)

The effects of these changes at the following mitosis have been seen chiefly in plants and animals treated with X-rays or by other special agents, since only then do they occur with measurable frequency. We then find that they may take place either before or after the chromosomes have divided during the resting stage. If before, then the changes apply to both the chromatids of each affected chromosome in the same way. We have "chromosome breaks". If after division, then the changes apply only to single chromatids. We have "chromatid breaks". These occur only when treatment has been applied towards the end of the resting stage.[1]

Another consequence of structural changes that is important genetically depends on the behaviour of acentric and dicentric chromosomes. Acentric chromosomes, like univalents at early first metaphase of meiosis, are entirely passive and are nearly always lost at anaphase. They never develop new centromeres. The centromere is evidently a specific and permanent body which cannot arise from anything else. Dicentric chromosomes divide in various ways. Their two centromeres, unlike the non-dividing centromeres of a bivalent, orientate independently. Evidently internal orientation or polarisation of the centromere is correlated with preparation for division and prevents co-orientation in pairs. If the two chromatids between them lie parallel no harm is done. The two centromeres pass to each pole with a loop chromatid between them. If, on the other hand, the chromatids make half a coil between the centromeres they are pulled out diagonally to make a cross, and unless they are very long they are likely to break under the anaphase tension at one or more points. Dicentric chromosomes cannot therefore be permanent at mitosis unless the length of chromosome between the centromeres is short enough to avoid coiling. And even then they will not usually survive meiosis under normal conditions, for the centromeres of the same chromosome would become co-orientated and therefore break the chromosome at anaphase.

It follows that the majority of structural changes damage the chromosomes that suffer them and are not therefore likely to survive. Those we find in nature are the ones that have survived and they correspond with types expected from experiment: deletion, inversion, interchange and one more complicated type, removal or *translocation* of an interstitial segment from one position and its insertion in another position in the same or a different chromosome. This last change is less common because it requires three breaks.

Apart from a large deletion or a grossly asymmetrical interchange, the results of structural changes cannot be seen from the shapes of the ordinary mitotic chromosomes. They are, however, characteristically shown by the chromosomes at pachytene in organisms that are hybrid for them—containing unchanged chromosomes and their changed homologues paired in their homologous parts. We then have a fold formed for a deletion, a loop for an inversion, a cross for an interchange, and more complicated configurations for more complicated changes (Figs. 9 and 10).

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[1] Mather, 1937.

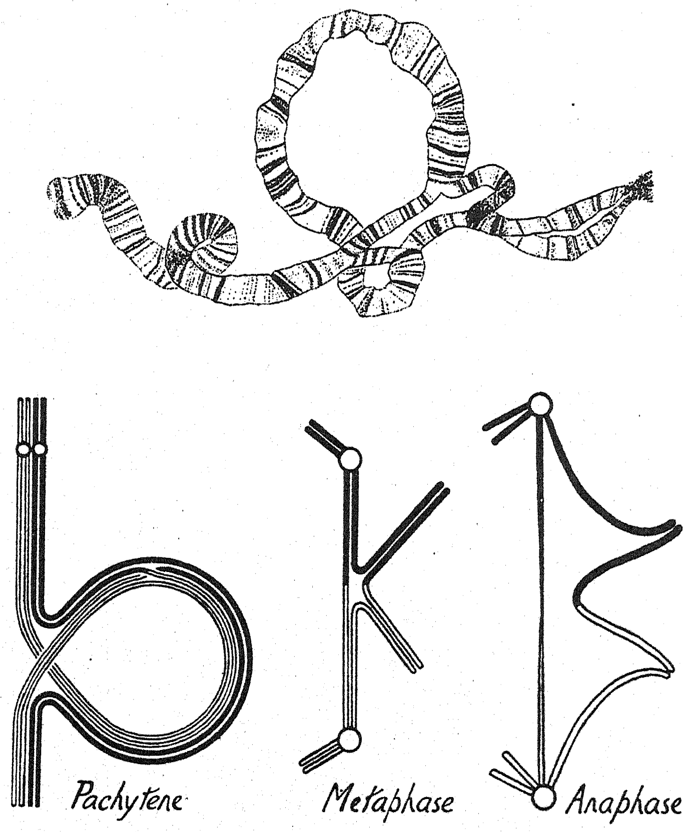

Fig. 10. Above, formation of a loop by pairing of two relatively inverted segments in the salivary gland cells of the cross of *Drosophila melanogaster* and *D. simulans* (Pätau, 1935). Below, the consequences of single crossing-over at meiosis in such an inversion hybrid with the formation of a dicentric bridge and an acentric fragment.

These arrangements are exactly mimicked in salivary and other gland cells in the dipteran flies. These undergo a perpetual prophase, neither mitotic nor meiotic, for the nuclei never divide again. Instead they grow to an immense size, and the chromosomes, stretched even longer than at pachytene, are reduplicated to form bundles of 16 or 32 threads, each chromomere of which owing to its multiplication appears as a transverse band. Attraction like reproduction is without limit: homologous bundles pair as single threads do in meiosis. In *Drosophila* the centromeres of all the chromosomes fuse. The configurations produced in hybrids are then just the same as at pachytene, and, although the cells have no genetic future, they provide the key to what is happening at meiosis in flies where the actual pachytene stages are beyond the reach of vision. They provide also the means by which gene arrangement can be compared in related individuals or species. The chromomere bands are so large that every group of them is characteristic and recognisable. The whole natural conditions of variation in chromosome structure are diagrammatically exposed to view (Fig. 10).

Let us now return to consider the consequences of these systems of pairing at meiosis in the hybrid. An interchange hybrid will have an association of four at pachytene (*AB–BC–CD–DA*, Fig. 9). When crossing-over takes place in all four pairs of segments of the interchange hybrid an association of four chromosomes is formed at diplotene which gives, with complete terminalisation, a ring at metaphase. If crossing-over takes place between three of them a chain of four is formed. These associations behave just like mechanically similar associations in a tetraploid. The difference in genetic content and in the genetic consequences of their movements has no effect on the movements themselves. We find the same linear, convergent, indifferent and parallel co-orientations. With complete terminalisation the convergent arrangement is the commonest. It alone can give genetically complete haploid combinations (*AB* and *CD* or *BC* and *DA*). These alone can survive; the others are defective and come to nothing. If crossing-over fails between the interchanged segments, as it does when they are short, two bivalents, *AB–BC* and *CD–DA*, will be formed. Segregating at random they will give the *competent* combinations in half the cells and incompetent ones (*AB* and *DA* or *BC* and *CD*) in the other half.

There is a third method by which interchange hybrids give defective gametes. If crossing-over takes place between the centromeres and the point of interchange (*b* and *d* in Fig. 9 (ii)) any orientation gives a regular separation and a competent combination for only two of the four chromatids at the chiasma. Half the effects of crossing-over in these interstitial segments are done away with.

Moreover if another interchange takes place to give a ring of six at meiosis another kind of segment is created (*x* in Fig. 9 (iii)). Crossing-over in this *differential* segment will also reduce the competent combinations to half. But those that survive are found to have suffered reverse interchange and the selfed progeny arising in this way have a ring of four instead of a ring of six.

Abnormalities thus result from three causes: from the interchanged segments being too short to have crossing-over, from the segments proximal to them being long enough to have crossing-over, and from the chiasmata resulting from crossing-over not being terminalised. Such are the causes of sterility in the interchange hybrid.

The inversion hybrid tells an altogether different story. Crossing-over between the relatively inverted segments (if they do not include the centromere) produces two new chromatids, one dicentric, the other acentric. At first anaphase the dicentric chromatid is stretched across the spindle, forming a bridge between the two groups of separating chromosomes, and the acentric chromatid is left passive on the plate. In a grasshopper, where the telophase nuclei are widely separated, the bridge is usually broken near the middle; in a plant, unless the bridge is short, it survives and can still be seen joining the second division metaphase plates. When, as in the eggs of *Drosophila* or the embryo-sac mother cell of a plant, the four nuclei that are formed at meiosis lie in a row instead of in a square, the two free arms joined to the dicentric chromatid pass to the inside two of the four cells. Since the end nucleus alone usually functions as the egg or spore nucleus, these do not show the results of crossing-over in an inversion so readily as the male nuclei, which are taken from all four products of meiosis.

One crossing-over prevents another near it but two crossings-over can take place in a long inversion. The results depend on whether the same or a different pair of chromatids are concerned in the two. If the same, one will compensate for the other: their chiasmata will be reciprocal, normal chromatids will be restored and no abnormality will be visible at anaphase. If a new pair cross over, complementary chiasmata will be formed. A double bridge and two fragments will be seen at anaphase. It can also happen that one chromatid crosses over with two different chromatids to give two disparate chiasmata. These will again leave a single bridge and fragment.

When in addition the dicentric chromatid crosses over proximal to the inversion, that is, between it and the centromere, a loop chromatid is formed returning to the same centromere from which it came. This leaves a fragment at the first anaphase and forms a bridge at the second. The statistical study of the frequencies of these different kinds of bridge formation therefore enables us to say what relationships exist between the successive crossings over. Sometimes the chromatids that have crossed over at one chiasma are more likely, sometimes less likely, to cross over at the next chiasma. The same properties are indicated by linkage studies in *Drosophila* and in the fungus *Neurospora*.

It will be seen that the results of crossing-over in short inversions are always disastrous to the chromatids that have crossed over. They inevitably lose their ends in the acentric fragment, and they may lose more in the breakage of the bridge. We must therefore make a distinction between real and *effective* crossing-over. Crossing-over may occur very frequently in inversions, but since its effect is so drastic its result will be either a drastic hereditary change or more usually it will come to nothing; the changed cells will die. Effectively, as in interchange hybrids, crossing-over is suppressed. It is suppressed *within* an inversion but *proximal* to an interchange. And an index of its suppression in both cases is usually the reduction in fertility of male hybrids.

CHAPTER VIII

HYBRIDS: DIPLOID AND POLYPLOID

SPECIFIC kinds of hybridity we now know have specific effects at meiosis. Can we use this knowledge to find out how the parents of hybrids are related? In the simplest cases we can. Most plants and animals that are not strictly inbred are hybrid for several structural changes, usually inversions or translocations. Crosses between species are usually even more hybrid. In extreme cases their behaviour leads to a new kind of result.

Occasionally two relatively inverted homologous segments, especially if they are short, instead of pairing in a loop, pair the wrong way round so as to continue the straight double thread on either side of them. Non-homologous genes therefore lie side by side and no crossing-over takes place within the inversion. In a similar way pairing may slip past a point of interchange where the exchange of partners should take place, the *AA* and *CC* systems of pairing extending at the expense of the *BB* and *DD* (Fig. 9 (ii)). Again non-homologous genes associate. This kind of aberration demonstrates an important principle. We saw that the partner chromosomes coiled round one another at pachytene. To do so they must develop a torsion. A piece of string under torsion will, if its ends are brought together, pair with itself. The association is due to torsion, not attraction. In a non-hybrid both forces work together to the same end. In a hybrid they are alternative, and where obstacles lie in the way of satisfying the homologous attraction the non-specific torsion draws dissimilar parts of the chromosomes together.

It is clear that the obstacles to correct pairing become greater where the differences are most numerous. This is shown most clearly, although indirectly, by the chromosome behaviour in the salivary glands of some *Drosophila* species. In *D. melanogaster* × *D. simulans* the differences are few and simple (Fig. 10). In *D. miranda* × *D. pseudo-obscura*, on the other hand, so many changes in arrangement have taken place that corresponding segments are scattered in different chromosomes and sometimes cannot be traced. The chromosomes in many cells entirely fail to pair. At pachytene they would probably pair at certain points and non-homologous torsion pairing would extend from these points. However this might be, very little crossing-over could take place; the chromosomes forming no chiasmata would be unpaired at metaphase. These crosses are highly sterile in both sexes.[1]

Such indeed is the characteristic behaviour in crosses between species. The pairing of the chromosomes is more or less incomplete at metaphase. It is also variable from cell to cell on account of variations both in the amount of true pachytene pairing and in the frequency of crossing-over in the paired parts. Thus while the chromosomes of *Allium fistulosum* or *A. Cepa* form one, two or three chiasmata, those of their hybrid range from none to three; about a quarter of the chromosomes form no chiasmata and are therefore univalent at metaphase.[2] At one extreme in the cross between *Brassica oleracea* and *Raphanus sativus* bivalents are rarely formed, while at the other in the cross between *Festuca pratensis* and *Lolium perenne* the chiasma frequency is scarcely reduced and the failure of pairing is as rare as it is in the parent species. These contrasts in crosses between pairs of species with the same chromosome number show that the genetic differences underlying the distinctions between these pairs are different in kind or enormously different in degree.

When crosses between species having an intermediate degree of abnormality are examined in detail the cause of the contrast is made clear. In *Lilium* hybrids the frequency of chiasma formation is reduced. And such chiasmata as are formed are largely between inversions. Inversions are known to impair the association at pachytene just as they do in the salivary glands. It is they therefore that reduce the frequency of chiasmata. The extent to which pairing fails is a measure of structural hybridity. Evidently the genetic differentiation of *Brassica* and *Raphanus* has been accompanied by structural changes in the chromosomes, that between *Festuca* and *Lolium* has not.

Since crossing-over is a condition of pairing of chromosomes, the numbers of chiasmata in the bivalents are always greater, in different individuals or different cells of the same individual, where there is a larger proportion of bivalents formed (e.g. in *Gossypium* crosses and in a maize mutant with defective pairing[3]). Where the chiasma frequency and metaphase pairing are greatly reduced, the distribution of chiasmata shows the effects of torsion pairing. Pairing begins in one part of the chromosomes, usually the ends, between homologous parts, and is continued by torsion elsewhere. Chiasmata are thus restricted to the ends in many hybrids such as those between *Triticum* and *Aegilops*. Any restriction of pairing also (for a reason we shall see later) causes a localisation of pairing and crossing-over (cf. Fig. 15).

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[1] Dobzhansky, 1937.
[2] Cf. Fig. 16.
[3] Beadle, 1933*a*.

Where almost all the chromosomes appear at metaphase as univalents the normal course of meiosis is entirely upset in one of three general ways. The simplest is that found only in certain moth hybrids (e.g. *Pygaera pigra* × *P. curtula*) where two effectively mitotic divisions replace meiosis. The chromosomes, all univalent, divide at both. A second type is that where all the univalents divide at the first division and two nuclei are formed which fail to divide again. A third type is that where the first division instead of the second fails. The chromosomes fail to come on to the first division plate. The spindle stretches as it would at a normal anaphase but instead of separating two equal groups it merely disperses one scattered group. Consequently one or several nuclei may be reconstituted. If one, then it divides to produce two equal nuclei at the second division. If several, then many nuclei with different and defective numbers of chromosomes are formed.

All intergrades occur between these last two types in plants, and they show that the difference between them is a simple one. Where the change in the centromeres of the univalents which enables them to orientate and divide takes place early enough in relation to the development of the first division spindle this first division is successful and the second is suppressed. Where the centromeres are too late the first division is suppressed. This difference between different organisms in the timing of the centromeres of univalents is found when there are only a few of them. When nearly all the chromosomes are univalent it dominates the conduct of division.

When most of the chromosomes are unpaired a regular result of meiosis can thus ensue from its failure as a process of reduction and its replacement by one or two mitoses. This *non-reduction* is a characteristic consequence of non-pairing in hybrids. Non-reduction results in the formation of diploid gametes. These are fertile and yield polyploid offspring, triploid if in one gamete, tetraploid if in both. Hence hybrid or allo-polyploids are produced, as opposed to the autopolyploids arising from non-hybrid diploids. The same result will follow failure of mitosis in a hybrid. Take the simplest instance, that of the *Raphano-Brassica* hybrid ($x=9$). The whole 18 chromosomes usually appear as univalents at meiosis, and the effective pollen grains and egg cells have this whole complement. Thus the diploid hybrid with two sets of chromosomes, *RB*, produces gametes *RB* from which offspring *RRBB* ($4x$) arise. At meiosis the *Raphanus* chromosomes pair with their identical mates and likewise the *Brassica*. Eighteen bivalents are formed, meiosis is regular and its products numerically and genetically uniform. The hybrid is giant; it is also fertile and true breeding as we should expect. It is functionally diploid (Fig. 23).

The behaviour of *Primula kewensis* is different and specially significant. The diploid hybrid is a cross between two species, *P. floribunda* and *P. verticillata*, each with 9 bivalents. The hybrid likewise has regular pairing, but if the members of each pair are different in only one segment the chance of recovering a complete and perfect set of one species amongst the gametes of the hybrid would be $1/2^8$. And this recovery would be necessary if translocations had taken place between all the chromosomes since their common origin.

Both these hybrids are sterile. But the sterility of diploid *Raphano-Brassica* is due to the irregular distribution of whole chromosomes while that of diploid *Primula kewensis* is due to the irregular distribution of their parts entailed by the perfectly regular distribution of the whole chromosomes themselves.

P. kewensis however produces tetraploid shoots by failure of mitosis, and like the tetraploid seedlings of *Raphano-Brassica* these are giant and fertile. But they are not absolutely true breeding. As we should expect, the chromosomes of opposite diploid parents occasionally pair as well as the identical mates from the same species. Cells sometimes have one, two or even three quadrivalents. Thus while usually the tetraploid *FFVV* gives gametes *FV*, occasionally it gives gametes *FF* or *VV* in regard to one or two of the nine chromosomes in the set; or if we take crossing-over into consideration, in regard to parts of one or two chromosomes. Thus an allopolyploid like *Primula kewensis* with imperfect differentiation of its chromosome sets characteristically shows a new type of variation arising from the segregation of differences between the chromosomes of its original diploid ancestors. And the diploid ancestors of an allopolyploid species may be very remote.

Now, it may be asked, how can the chromosomes of *verticillata* so generally fail to pair with those of *floribunda* in the tetraploid although they pair regularly in the diploid? We saw that in many diploid hybrids the chromosomes pair regularly at metaphase in spite of obstacles to complete pairing at pachytene. We also saw that pachytene pairing must be much more rapid where there are no such obstacles. When therefore there are four chromosomes of each kind capable of pairing, two somewhat different in structure from the other two, we should expect the similar pairs to be so quickly associated that the dissimilar pairs would come together only occasionally. When chiasmata come to be formed the discrepancy is likely to be exaggerated, very small segments falling apart without chiasma formation. Thus *competition* in pairing will give rise to what may be described as *differential affinity*. Dissimilar pairs of chromosomes that are capable of association in a diploid, where there is no competition, will fail to associate in a tetraploid, where each has an identical mate.

The consequences of competition are shown in the analysis of polyploids as well as in their synthesis. Most flowering plants can give rise occasionally to seedlings by "haploid" parthenogenesis. That is to say the egg cell with a reduced number of chromosomes develops directly without fertilisation. An allotetraploid *Nicotiana Tabacum* which regularly forms $2x$ bivalents and no quadrivalents gives rise in this way to a diploid which has several bivalents. Chromosomes pair in this diploid in the absence of competition which never pair in the tetraploid. The hexaploid *Solanum nigrum* ($6x=72$) with no multivalents gives by parthenogenesis a triploid ($3x=36$) which has complete pairing of two sets of chromosomes. Similarly it often happens that two species, hexaploid and diploid, like *Prunus cerasifera* ($2x=16$) and *P. domestica* ($6x=48$) crossed give a hybrid which behaves like a regular allotetraploid species, forming the diploid number of bivalents.

It is not surprising therefore that allopolyploid species are liable to occasional lapses from their excellent diploid behaviour. Chromosomes of different sets pair and cross over, secondary segregation of ancestral diploid characters takes place and a new kind of variation appears. This is most frequent in relatively new polyploids like *Nicotiana Tabacum* and *Triticum vulgare* and leads to a different variation system from that of diploid species.

The kinds of polyploid species of plants illustrate in several ways the processes of natural selection to which their variations have been subject. Most such species are allopolyploid. A few are autopolyploids, and they often occur side by side with their diploid ancestors. These autopolyploids are of two kinds. They may depend largely on vegetative reproduction, in which case the lower fertility of the original autopolyploid is of little account. This is true in moderate degree of tetraploids like *Tradescantia virginiana* and in an extreme degree of triploids like *Lilium tigrinum* which exist purely as vegetative clones. Alternatively they may change the pairing habit of their chromosomes. The number of chiasmata may be reduced to one for each chromosome so that no quadrivalents can be formed. This happens to a varying extent with the tetraploid species of *Tulipa*.[1] The same result can be attained in another way. The species *Dahlia variabilis* ($8x=64$) is functionally an autotetraploid. That is to say it has random segregation of genes in fours and forms frequent quadrivalents. Nevertheless meiosis regularly yields 32-chromosome gametes. This is made possible by the regular formation of one chiasma in every chromosome arm and its regular terminalisation. The quadrivalents are therefore always rings and these co-orientate convergently to give even segregation.[2] Thus reproduction from seed means inevitably selection for fertility and this is achieved in an autopolyploid by abolishing multiple pairing. How common this type of selection may be in plants with smaller chromosomes we do not yet know.

Both in auto- and allopolyploid forms selection also apparently acts to remove the original gigantism, partly or entirely; polyploid species may be even smaller than their diploid ancestors. In *Silene ciliata* two similar types exist in different localities, one with 24, the other with 192 chromosomes. In such species important genetic changes must be necessary for the behaviour in polyploid cells to be adapted to the reproductive needs of the plant. The absence of polyploidy in certain groups of plants, such as *Ribes*, is less likely to be due to a failure to produce polyploid shoots or to a regular perfection of meiosis than to the failure of these genetic adaptations.

[1] Upcott, 1939.

[2] Lawrence, 1931 *b*.

CHAPTER IX

CHANGE OF PROPORTION

FAILURE of pairing of two chromosomes is found at meiosis in most diploid plants and animals from time to time owing to one or more of several conditions such as senility, abnormal temperature, hybridity and even a mutant genotype. Hence germ cells arise with one chromosome too many or too few. In the higher plants where the haploid generation goes through several cell divisions those cells with a chromosome missing from the haploid set never go any further. They die. Those with the extra chromosome live, and often provide functional gametes, especially on the female side where the haploid generation is less important. This difference of behaviour may be seen most readily in species of *Oenothera*, where $x+1$ and $x-1$ germ cells are regularly produced and give rise to trisomic ($2x+1$) offspring only. This natural selection tells us that the whole haploid set is necessary for life and development in any diploid organism. In fact the haploid set may be defined in this way as that group of chromosomes which is necessary for the full development of the haploid generation or when added to another similar set is necessary for the full development of the diploid generation. Clearly this is bound to be so, for any chromosomes that can be lost without disadvantage from the haploid set are bound to be lost by chance irregularities sooner or later. The haploid set is an adaptive unit. The selection works at once on the newly formed pollen grains. Only once has an $x-1$ pollen grain been seen to go through its first mitosis (in *Uvularia*) and then it was still exceptionally attached to a complementary $x+1$ pollen grain.

We should expect, in view of this defect of the $x-1$ germ cells, to find that $2x-1$ zygotes are never produced. This is true except where the missing chromosome is extremely small, as happens in some species of *Drosophila* or where competition is eliminated by killing the normal germ cells with X-rays in *Zea Mays*. Nor is it surprising to find that such *monosomic* zygotes are of feebler growth than the straightforward diploids. It is, however, something new and significant when we find that the complementary type of trisomic plants and animals are also of feebler growth; and further that each of the different chromosomes of the haploid set when it is present in excess gives a different type of abnormality. In the tomato (*Solanum Lycopersicum*) with twelve pairs of chromosomes, twelve kinds of trisomic occur, recognisably different in the shape of their leaves.

When we recall chromosome behaviour at meiosis we see however that this specific and different physiological action of each chromosome is not in fact an isolated property: every member of the haploid set has a specific and therefore a different property of attracting a mate at meiosis. The physiological differentiation of the chromosomes could have arisen in a sexually reproducing organism only if it was coupled with a mechanism securing the segregation of similar chromosomes to opposite poles in meiosis. And both must depend on the specific and different properties of the individual particles which make up the chromosome chain and which associate independently at pachytene in polyploids, as the changes of partner they undergo most clearly demonstrate.

These considerations lead us further. If the differences between the chromosomes depend on differences between the chromomeres which make them up, perhaps losses and gains of single chromomeres will also produce a physiological effect. There are now a large number of observations bearing on this question in *Drosophila*. We find that losses of certain chromomeres are almost as injurious to the organism as losses of whole chromosomes. When the deficient zygote produced is hybrid for the loss (corresponding to $2x-1$) it is of poorer and abnormal growth. When it is pure for the loss (corresponding to $2x-2$) it dies at any early stage. The condition is lethal. In plants such deficiencies affect the haploid generation as well. In *Zea* they kill the pollen and injure the eggs.[1]

Now it will be seen that loss of a chromomere or a small segment of chromosome, which we earlier referred to as deletion, will behave in inheritance like one of Mendel's alternative factors. The pure form is lethal while the hybrid crossed with the normal will give a 1 : 1 proportion of the hybrid and pure types in the progeny. Several different mutations of *Drosophila* such as "Notch" wings are known to be due to this kind of change. The gap can be seen in one of the pairing chromosomes in the salivary glands of the hybrid just as it can be seen in the pachytene chromosomes of *Zea* at the place expected from study of the factor linkages in breeding experiments.

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[1] Rhoades and McClintock, 1935.

But all the different chromomeres are not equally indispensable. They are different in their work and also different in their importance. There are even some whose loss has no observable effect on the organism. It can be pure for this loss and show no defect. Evidently such chromomeres or genes are *inert*. They are physiologically so much useless ballast. No chromosomes of the haploid complement can, by the definition we used earlier, consist entirely of such genes; all chromosomes probably have a few of them, since they can be lost only by a chance deletion which does not include any valuable neighbours. They are, however, so frequent that we must suppose they often have some use. Later we shall see that parts of chromosomes which have no physiological use may be needed mechanically. Parts of chromosomes where inert genes are crowded may be recognised by their differential reactivity under special treatment. The inert parts, for example, may be made to stain more deeply at telophase in mosses and regularly stain less deeply in the salivary gland cells of *Drosophila*. This is important not merely as a practical means of detection but because it shows that the staining reaction and the physiological action are related. Both perhaps depend on the presence or arrangement of side chains attached to the main chromosome thread.[1]

Entirely inert chromosomes have been found in many species in Hemiptera and Orthoptera as well as in flowering plants. They are not members of the haploid complement and they vary in number in different individuals, one, two, three or more of a kind. They are usually smaller than any members of the normal complement. Such supernumerary fragment chromosomes, as they have been called, may be present to the number of 20 in some strains of *Zea Mays* and also in the only known stocks of *Tulipa galatica*. We then find that they vary in number in different mitoses. The reason is that the centromeres of these chromosomes are not accurately synchronised with those of the ordinary complement. They may divide too early or too late. This may be due to their small size or to an abnormal surface action of their inert genes.

How do these supernumeraries arise? Breakage of bridges following crossing-over in inversions is continually taking place in most organisms. If the centric fragment passes to the same pole as its unbroken sister and happens to be inert it will be capable of surviving as a supernumerary. Since small inert extra chromosomes have been found in some forty species of plants and animals it seems likely that the part of the chromosome near the centromere is usually inert.

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[1] Heitz, 1935; Darlington and La Cour, 1938.

The plants with this enormous excess of inert chromosomes show no external abnormality and the freedom with which they vary in number shows that no selection is working against them. Quite otherwise is the condition with extra active chromosomes. Often trisomic plants of poor growth will sport a shoot of normal and vigorous diploid tissue. Such a sport will soon dominate the situation and overwhelm the abnormal plant from which it was derived. Trisomic shoots appearing on diploid plants on the other hand are almost unknown, monosomic ones entirely so. The reverse change is always to be inferred. Any irregularity in cell division is controlled by the regularity of *cell selection.*

Since all somatic changes in number arise from the same type of mechanical defect at mitosis it is evident that the different types of cells compete in the meristem. The normal is then nearly always selected at the expense of the abnormal by a departure from the strict rules of development expected in a genetically uniform tissue. The result of this is shown most strikingly by high polyploid mosses and flowering plants with odd chromosomes beyond a multiple of the basic set. These odd chromosomes are lost in development: the combination of mitotic errors and cell selection produces a genetic regulation of the plant.

Thus a normal type of growth in all groups of organisms is produced by a modal chromosome constitution which is what we call haploid in the gamete and diploid in the zygote. Further this modal constitution is adaptive; it is actively maintained by selection and must therefore have been originally produced by selection of variable combinations. This modal adaptation or adjustment is known as *balance.*

The kind of physiological processes underlying the attainment of balance can be shown by considering the actions of particular genes.[1] *Dahlia variabilis* behaves as an autotetraploid in inheritance. Each gene can be present in none, one, two, three or four doses, none being the pure recessive, four the pure dominant.

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[1] Lawrence and Scott-Moncrieff, 1935.

Take the combinations of two genes affecting pigment production, B and I, in plants which are purely recessive for all other such genes. The pigments concerned are the anthocyanins, pelargonin and cyanin, and the flavone apigenin. We have the following combinations:

b_4i_4: no pigment—white petals.
Bb_3i_4: cyanin alone—chocolate petals.
$b_4I_2i_2$: apigenin alone—ivory petals.
$Bb_3I_2i_2$: cyanin + apigenin—purple petals.
Bb_3I_3i: cyanin (+pelargonin) + apigenin—magenta petals.
$B_2b_2I_2i_2$: pelargonin (+cyanin)—carmine petals.

We see that B and I, which separately or together in low dosage produce cyanin and apigenin, in increased dosage produce pelargonin and at a certain threshold suppress the flavone production altogether. The reason for the relationship in this case is indicated by other evidence to be the development of the anthocyanins and flavones from sugars through a common antecedent, and the greater divergence of pelargonin than cyanin from this common antecedent.[1] A change of quantity as well as a change of proportion leads to a change of quality in the product. Balance therefore depends on absolute quantities and on relative quantities of individual genes.

Most changes of balance due to gains or losses of whole chromosomes, or of small parts which behave as Mendelian changes, are deleterious simply because they have usually occurred before and would themselves have become the mode if they had not been deleterious. They have been tried in the past and found wanting. But changes in balance nevertheless have occurred in the past which were tried and found good. They have happened chiefly by structural change and by polyploidy.

When a small segment x is translocated from a chromosome A to a chromosome B a hybrid nucleus is produced with four chromosomes which we may call $A^xB.AB^x$. This will produce gametes A^xB^x as well as AB from which pure zygotes with four x segments will arise, $A^xA^xB^xB^x$. In a word the x segment has been *reduplicated*. The type is unbalanced in regard to a single segment. Such new types have arisen in *Drosophila melanogaster* where reduplication of a particular segment produces a narrow "Bar" eye and a double reduplication a type of lower vigour with an even narrower eye known as "Super-bar". When the structure of the salivary gland chromosomes in different *Drosophila* species is examined, small *repeats* of similar sections are found, indicating that this kind of change has taken place freely in the past. Thus we cannot suppose that the haploid set contains one gene of every kind. It must contain only one gene of some kinds, but of others two, three, four, or more. In fact the distinction between diploid and polyploid species in general will be less in the number of genes of each kind than in the number of chromosomes of each kind.

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[1] Robinson, 1936.

The existence of reduplications and replacements within the haploid set of genes warns us that many identical pairs of genes need not be Mendelian alternatives and many alternatives need not be identical or even closely related in origin. Alternative inheritance of genes depends no less on the identity of the genes whose inheritance is being studied than on their linear sequence. It is a function of position in the chromosome.

The consequences of reduplication are seen at meiosis in the flowering plants, where it often happens that two reduplicated segments within the same set cross over and form a chiasma. In fact in haploid plants of *Oenothera* it happens that two chromosomes form chiasmata. Again we see the definition of a haploid set is not a matter of absolute analysis but of functional convenience.

This leads us to consider whether changes in balance of chromosomes of the basic haploid set are not possible. Related species like *Crepis capillaris* ($n=3$) and *C. tectorum* ($n=4$) often have different basic numbers. But it is not necessary to suppose that any serious change of balance is involved in the change of number. Four chromosomes can be derived from three by a change akin to simple breakage. The fourth chromosome may begin as an inert supernumerary which afterwards by translocation of an active segment becomes a necessary part of the haploid complement. Since so many species are known with such supernumeraries, this method of changing the chromosome number of the basic set is probably the usual one.

A second method of change involves a change of balance and consists in the mere reduplication of whole extra chromosomes. In *Datura Stramonium* ($n=12$) trisomic plants produce among their seedlings tetrasomics which have two extra chromosomes both of the same type. This happens only with a few of the smallest extra chromosomes. They can have 11 bivalents and one quadrivalent, or 13 bivalents. These plants being much more seriously unbalanced than the corresponding trisomics are of poor vitality and scarcely set seed. However when we begin with a tetraploid the unbalance produced by two extra chromosomes is not so violent. The proportional upset corresponds with that in a trisomic diploid. It is not surprising therefore that it has been possible to derive a new type in this way from an allotetraploid species, *Nicotiana Tabacum* ($4x=48$). This new form is hexasomic, having an extra pair of chromosomes derived from crossing with *N. sylvestris*. One type of chromosome is represented six times and the other eleven four times. Its complete constitutional formula may be represented as $2n=4x+2=50$. It has a new or secondary basic number of 25, and its external appearance diverges from that of species with the old primary number of 12. Such a plant may be described as a *secondary polyploid*.

This type of change, which has been carried out with several species in experiment, has no doubt played an essential part in the origin of many species. It will often determine an important change of form at the same time as intersterility with the old type. When there appears in a group a new basic number which is not a direct multiple of a lower one we may therefore suspect this kind of change. But other changes can be responsible. Mere fragmentation without change of balance (Fig. 19), either directly or by combination of diploid species with different basic numbers giving dibasic polyploidy, as in *Saccharum* and *Narcissus*, must be excluded. We have therefore to apply several tests, of which two may be mentioned.

In the first place the change must be a change in a polyploid, and in a group in which changes in the basic numbers of diploid species occur rarely, if at all. This is true of many groups of flowering plants, such as the Rosaceae.

In the second place a special relationship of the chromosomes must be seen at meiosis. In allopolyploids where the chromosomes are small and contracted to a spherical shape the homologous bivalents do not form multivalents but come to lie next to one another on the metaphase plate and closer together than do the non-homologous chromosomes. Groups of three or four bivalents may appear in this way in hexaploids or octoploids, but the associations are variable, depending on the chances of the right pairs lying near one another during the preparatory stages of metaphase when the bivalents all come close together. Evidently a specific attraction, like that which brings chromosomes together at prophase, is apparently acting at a distance to modify the even equilibrium on the metaphase plate. It does not show itself so readily at mitosis, or at meiosis when the chromosomes remain long, because presumably they offer more resistance to movement.

In a secondary polyploid we can recognise the numbers of chromosomes of each type by their association in this way. Thus in *Dahlia* all the species have a basic number of eight[1] except one, *D. Merckii*, which has 36 chromosomes. Its haploid complement of 18 is not derived from one of 16 by fragmentation, because there are two associations of three equal bivalents together with six associations of two bivalents. Its formula is:

$$2n = 4x + 4 = 36.$$

This species stands alone in the genus in its morphological character. It is evidently a secondary polyploid.

Taking even larger groups we can acquire not less certainty but more where the secondary polyploid type is absolutely constant. This is the case with the Pomoideae. The rose group of the Rosaceae show a constant basic number of 7, the apple group, embracing hundreds of species, shows an equally constant basic number of 17. Chromosome behaviour makes it clear that the formula of the apple is

$$2n = 4x + 6 = 34.$$

It is to this change in balance from 7 to 17 that we must suppose the apple and hawthorn owe their distinctive fruits.

The secondary polyploid therefore has a secondary balance. The original balance has no absolute validity. It merely represents a tested combination, a tested proportion. Just as the wild type of genes work better under wild conditions than the mutant types usually do, so the wild type of balance works better than a new type of balance. If the wild type did not do so it would soon cease to be the wild type. The inefficiency of most mutants is a corollary of the efficiency of natural selection. When the mutant gene or secondary balance appears which is not inferior it survives and a new step in evolution is made.

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[1] Lawrence, 1931 *b*.

Naturally we cannot expect that the evolutionary story will often be as simple as this, and no great interest attaches to the tracing of phylogenies which are more conjectural. No doubt many are intermediate between the simple types we have chosen for demonstration. It is merely necessary to establish the principle that evolutionary changes can take place by large as well as by small changes of balance and that alteration of the basic number of chromosomes may occur with or without such changes.

CHAPTER X

THE ATOM OF GENETICS

We are now in a position to discover more exactly what some of the hereditary differences that are subjected to breeding tests mean in terms of the chromosomes whose changes are responsible for them.

An interchange hybrid $(AB+CD)$ $(BC+DA)$ produces two kinds of regular gametes, the same as those from whose fusion it arises, $AB+CD$, and $BC+DA$ (Fig. 9). It consequently produces offspring of three kinds $(AB+CD)$ $(AB+CD)$ (pure), $(AB+CD)$ $(BC+DA)$ (hybrid) and $(BC+DA)$ $(BC+DA)$ (pure). It produces them in the proportion 1 : 2 : 1, the Mendelian proportion for an F_2. But it also produces unworkable combinations by what is called *non-disjunction* of the pairing segments when the co-orientation of the ring of four is parallel instead of convergent. These combinations are defective and sterile. The interchange hybrid is therefore recognisable by its partial sterility and we might ascribe the inheritance of this sterility as due to a gene difference *S-s* which in the hybrid condition gave sterility although *SS* and *ss* were fertile. In fact this kind of explanation was used before the meaning of the chromosome behaviour was understood.

A more widely known type of Mendelian difference is that produced as we saw by a deletion (or duplication) of a small segment. Such deletions were at first described as gene mutations before closer linkage studies showed them to be due to loss of a small segment, a conclusion whose rightness was finally demonstrated by direct study of the salivary gland super-chromosomes.[1]

But recent cytological study has gone much further than this in revealing the material basis of variation. The inversion of a segment of the *X* chromosome of *Drosophila melanogaster* (arising from X-ray treatment) produces in the true-breeding condition a roughness of the eye surface. This may be regarded as a recessive mutation located at one of the points of the breakage which led to the inversion. But it happened that, in a stock of flies hybrid for this inversion, a reversal of the inversion took place; the new change was the exact reciprocal of the original structural change. At the same time the mutation disappeared. Evidently the genetic change was directly determined by the change in the linear order of the particles at the break. It could be due only to the physiological action of one gene depending on the proximity of another.[1]

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[1] Muller and Prokofyeva, 1935.

How important this principle of the *position effect* may be we do not know, but it probably applies to many pairs of genes in linear proximity in the chromosomes in *Drosophila* and presumably therefore elsewhere. When an interchange takes place a genetic difference appears and the pure interchange type may even be lethal. The behaviour of the Bar gene already referred to illustrates the point in another way. As we saw, Bar is due to the reduplication of a segment. Two segments immediately adjoining repeat one another, like *abcdcdef*. When the fly is pure for Bar it sometimes happens that crossing-over takes place between the right *cd* of one chromosome and the left *cd* of the other, so that a new chromosome is produced with three *cd* segments. A fly hybrid for normal and this "Super-bar" then has four *cd* segments like a simple pure Bar fly. But it shows the Bar character more strongly. It has fewer eye facets. The relative position of the *cd* segments affects their action.

We have already seen that the individual particles or genes making up the chromosome, although units of inheritance separable by crossing-over, are not units in regard to physiological action. They interact throughout development. We now see that they interact even inside the nucleus. They are balanced or adjusted therefore in "normal" or "wild-type" members of the species, not only in their proportions but also in their positions on the chromosomes. Even more important, we see that Mendelian differences may be determined in three recognisable ways: by mechanical defects in segregation; by proportion changes; by position changes. All these three are determined by changes in the linear order of the particles, by *intergenic* change.

It might indeed be thought that such changes between genes were important enough in their action to account for the whole range of variation observed now and inferred in evolution. But this cannot be true. Changes of arrangement and balance can effect genetic changes only by virtue of differences between the particles that are rearranged or rebalanced. The specific properties of mutation known in many genes justify this conclusion. The specific attractions between homologous particles in the chromosomes bear it out. Specificity implies diversity.

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[1] Grüneberg, 1937.

The genes making up the chromosomes must therefore be different. They must also be capable of giving rise to one another by their specific and limited steps of mutation unless we assume a special creation of each gene. There must therefore be a process of *intragenic* change, change which is qualitative and molecular, as well as one of intergenic change which is structural and supermolecular.

This distinction is strict and indisputable in theory, although in practice it only separates the known from the unknown. We know which mutations are undoubtedly intergenic; we do not know which are undoubtedly intragenic. There is no means of distinction by physiological effect and we cannot see whether a single gene may have been turned the other way round or have lost an attached radical.

Let us now consider how the gene is inferred. Mendel ascribed the cause of the discontinuities which he discovered to incorporeal "factors". As soon as it became possible and necessary to relate these factors to particular cells it also became possible and necessary to allow them a material character. This Johannsen did by giving them the name of genes. These Mendel genes were obviously units of recombination and mutation. Their position and structure Johannsen did not define. But he went so far as to suggest that the genotype was "the sum total of all the genes". He was assuming implicitly that the whole hereditary substance consisted of particles analogous to those whose differences made the direct inference of genes possible. He was also assuming, and again implicitly, that there were units of mutation which corresponded one to one with the units of heredity.

These implications of the Mendel gene were partly made clear by Morgan.[1] The chromosome was shown to be the vehicle of heredity. The chromomere of cytology showed particulate inheritance; the segregation of differences showed particulate variation. The two were consistent and provided a theoretical model on which nearly all predictions could be based in experimental practice. The gene became the unit of crossing-over.

Later work has entirely vindicated the concept of the Morgan

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[1] Morgan, 1926.

gene as a unit of inheritance. But it has equally invalidated this particle, or indeed any particle, as a unit of variation, for this reason: any one particle can cause variation in several different ways, by changes in quantity, in quality and in position. Further the co-existence of these three types of variation affects the practical use of crossing-over as a means of determining the unit of inheritance, in this way: an inversion may cause a mutation and at the same time suppress crossing-over within the inverted segment in any organism hybrid for the change, i.e. in any organism in which the effects of crossing-over could be detected. If there is another mutation within this segment the two will appear as a single unit of crossing-over. The suppression of crossing-over by structural hybridity and the position effect therefore destroy the unit of crossing-over as a reliable index of the gene.

These conditions are of practical importance in two other ways. When a chromosome, or part of one, is wholly inert and shows no variation within the species, how are we to represent its structure in terms of genes? When a differential segment in an interchange hybrid (*x* in Fig. 9 (iii)) never crosses over with its homologous segment although they may differ in genetic action, again, how are we to represent its structure?

These questions can be answered only if we can control the mutations of the gene and relate them to the observable structure of the chromosome, and thus make its diagnosis independent of the tests of crossing-over and undefined mutation.

This has been done by Muller's introduction of the new technique of X-ray treatment. The distal end of the *X* chromosome in *D. melanogaster* contains a group of chromomeres, changes in which affect the type of bristles on the thorax, producing the so-called "scute" mutations. The number of bands in this region may be determined most exactly by ultra-violet photographs. This number will be a minimum estimate, since some bands may be too small for resolution. The number of breaks which can occur in the same region under the influence of X-rays can be determined by examining the chromosomes of all flies affected by treatment, and by testing the viability of derivatives with different recombinations of breakages. The number of different points of breakage shown by specific physiological effects is not less than the number of chromomeres seen in photographs.[1]

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[1] Muller and Prokofyeva, 1935.

The unit of behaviour in the chromosome, the atom of heredity, can therefore be defined without regard to crossing-over. It is a visible particle which is also a unit of X-ray breakage. A particle subjected to this double test can legitimately be described as a gene, the Muller gene. The differences seen between individuals, inherited in a Mendelian way and behaving as units of crossing-over, cannot be treated as due to specific changes in these genes until it is known that they are not changes of position or proportion. They must remain Mendelian factors, factors whose origin is probably in most cases (especially where the change arises with a specific mutation rate, or is regularly reversible or occurs in a multiple series) an intragenic change, but whose nature must without cytological tests be left undefined.

Nor can we say that particular observed chromomeres are genes without genetic tests. The Muller gene depends for its validity on the double test. Armed with this decisive weapon we can now attack the hitherto evasive problem of the gene structure of chromosomes which are beyond the reach of crossing-over and mutation. Since genes correspond with chromomeres or parts of chromomeres wherever it has been possible to test them and since all chromomeres share with all genes the same essential properties of attraction, reproduction and linear arrangement, we can say that all chromomeres or parts of chromosomes, irrespective of the possibility of testing their recombination by mutation and crossing-over and irrespective of their having any physiological action, are composed of genes. These dynamic tests are limited by circumstances. The static test of visibility is unconditional and therefore alone capable of universal generalisation.

Different genes differ in size. The same genes also may appear to occupy different spaces owing perhaps to varying surface conditions. Hence many different estimates of the sizes of genes.[1] However the smallest space it can occupy will give a maximum estimate of the size of the gene. It is found in the mitotic chromosome which is also more exactly measurable than any other gene aggregate. Dividing the number of chromomeres of the third chromosome of *Drosophila melanogaster* visible in the salivary gland nuclei (say 2000) into the volume of the metaphase chromatid of this chromosome at mitosis (say 60,000,000 cu. $m\mu$) we obtain the value of $(30\ m\mu)^3$ for the average volume for the gene, together with the minimum space into which it can be fitted. This is the size attributed to the largest particles of plant viruses. We shall return to this analogy later.

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[1] Waddington, 1939.

The correspondence of visible particles and units of breakage gives us the answer to the question as to how differential and inert segments are made up. They consist of genes whose number may be estimated from the comparison of the number of their chromomeres with that in chromosomes whose gene content can be directly tested. It follows that inert segments of chromosomes in *Drosophila*, *Zea* and elsewhere must contain large numbers of genes which have mutated to inertness. It also appears that in doing so these genes have lost their capacity of mutating back to an active form. Inert genes have lost the reproductive instability as well as the reactive capacity characteristic of their working progenitors.

Recapitulating, there has been a contradiction of method in the inference of the gene, a contradiction inherent in the technical difficulties of investigation. It was at first assumed (very properly, on Occam's principle) that a particulate heredity implied particulate variation. We now know it does not. Visible particles can change in more than one way to produce hereditary variations. Some of these ways prevent such particles behaving as units of crossing-over. It is only possible therefore to take a unit of breakage by X-rays as having an unconditional validity. Such an atom of heredity shows a one-to-one correspondence with the observed particle. It is the gene of physics, biologically absolute.

This gene is a unit of heredity because it is mechanically separable from other genes in heredity, that is, in cell division. It is not and (unlike pre-Mendelian physiological units) was never supposed to be a unit in development. The whole of development consists in the interlocking reactions of genes, beginning inside the nucleus with the position effect and ending in the relationships expressed by the general principle of balance. The great achievement of genetic analysis has been in reconciling these two apparent contradictions in the properties of the genes, their independence in heredity and their integration in development.

CHAPTER XI

CHROMOSOME MECHANICS

NUCLEAR division, both mitosis and meiosis, consists of a series of co-ordinated changes and movements in and around the chromosomes. The co-ordinations seem to be, some of them, inherent in the system; and others, capable of being broken down in special circumstances. The information to be gained from these co-ordinations and breakdowns, combined as they are with a great array of known structural and genotypic conditions and with certain physical experiments, enables us to infer the agencies at work.

Changes in shape of the chromosomes are, as we have seen, due to internal movements in the chromosome thread—the spiralisation cycle. This cycle consists in mitosis of the assumption of a regular system of coils in each chromatid whose diameters increase and whose number decreases, both before the metaphase rod shape is assumed and while it is disintegrating as a *relic coil* at telophase and the following prophase. Why, it may be asked, should this uncoiling of the chromosomes of one mitosis be postponed to the next? The rate of uncoiling of different parts of the same chromosome is unequal. This shows that it depends on the chances of spatial distribution, that uncoiling is indeed limited by the confinement of the chromosomes in a restricted space, the resting nucleus. They are not free to move in response to their changing internal stresses as though they were *in vacuo*. They show a lag therefore in their adjustments to these stresses which may be compared to the hysteresis of non-living systems.

At meiosis each chromatid similarly assumes an internal coil, but here we can see in the larger chromosomes that within the *major spiral* another *minor spiral* is developed, a spiral of smaller diameter which no doubt begins to be formed when the major spiral has reached a certain diameter. Whether the slenderer mitotic chromosomes also include both orders of spiral formation we cannot yet say.

Since, in spite of the different amounts of coiling to be done, large and small chromosomes spiralise at the same rate, it is clear that this coiling is not conditioned externally by a method involving rotation of the ends. It must be directly due to an internal change which compensates for it spatially, rendering a rotation of the ends unnecessary. This argument is clinched by the fact that ring chromosomes without any ends (resulting from crossing-over between translocated segments) are capable of coiling and uncoiling as freely as rod chromosomes. Such a compensating system of coiling we may describe as a *molecular spiral* whose torsion must change subject to changes in the substrate.

What changes take place in the substrate are shown by the external movements of the chromosomes. The first and simplest of these is that at the early prophase of meiosis. We have seen that this may be described as the result of an *attraction* which is specific and exists only between pairs of genes. This attraction is satisfied at mitosis by the previous division of each chromosome into two chromatids. At meiosis, prophase begins before the chromosomes divide. Corresponding pairs of chromosomes therefore come together to produce the same equilibrium as that in mitosis. When later they divide, the chromosomes fall apart. The same attraction works therefore at all stages in the prophase nuclei of mitosis and meiosis, and meiosis is distinguished from mitosis by the *precocity* of the beginning of prophase in relation to the division of the chromosomes. This initial precocity has its effects on all the subsequent stages of meiosis and later we shall see how their variations provide us with a test of the theory.

It need not be supposed that the primary specific attraction between genes acts at any great distance, since the chromosomes are brought together in pairing by their chance proximity at a few points from which the pairing spreads. The residual attraction which is responsible for secondary pairing and is also specific to like pairs of bivalents on the other hand seems to be exerted at a considerable distance although it may be derived from an earlier close association.

Between the pairs of threads, chromosomes or chromatids, associated by the primary attractions there exist at all stages repulsions of varying strengths. They express themselves not by violent changes, since they are always acting, but rather by the maintenance of uniform spacing of the chromosomes in the prophase nucleus, on the metaphase plate and on the anaphase spindle. This repulsion is to be expected from the *surface charge* on the particles of an amphoteric electrolyte in a substrate not at its isoelectric point. It is analogous to the repulsion which preserves the suspension of colloidal particles. Its variation is to be expected from variations in the *p*H of the substrate. If, as there is reason to suppose, the chromosome is a chain molecule, then variation in repulsion might be expected to produce the changes of shape we have seen in the spiralisation cycle by changing the equilibrium between successive side chains.

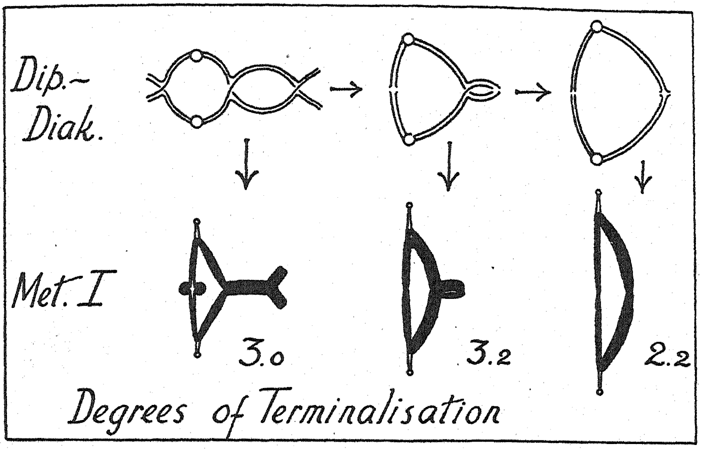

Fig. 11. Above, the stages of terminalisation in a bivalent with three chiasmata. Below, the metaphase configurations produced when terminalisation is interrupted at early or late stages. The three types are *Fritillaria*, *Tulipa* and *Campanula* in plants, or *Chrysochraon*, *Chorthippus* and *Acridium* in animals.

The evidence of this inevitable co-ordination is to be obtained from the later stages of prophase. The occurrence of the movement of chiasmata then shows us that the centromere has a stronger effect than the body of the chromosome, owing presumably to its special chemical character. In various abnormal animals and plants, e.g. the male *Macronemurus* and the male-sterile sweet pea (*Lathyrus odoratus*) a higher terminalisation is correlated with a greater spiralisation of the chromosomes. The body repulsions of the chromosomes can be shown to assist in this movement, since the chiasmata of two ring bivalents in *Tulipa* show more movement if they are interlocked than if they are free (Fig. 11).

The greatest advantage is to be had from comparing the behaviour of bivalent chromosomes inside the prophase nucleus with that on the metaphase spindle. Inside the nucleus the bivalents show no orientation. On the spindle all their pairs of centromeres are co-orientated axially. When an orientated structure is obvious in the spindle before the chromosomes come on to it we must suppose that the co-orientation of the chromosomes depends on that of the spindle. Since the centromeres of the bivalents which become orientated move farther apart, i.e. do work, we must suppose that they become orientated because by doing so they reduce their potential energy. Further, since they can do this work only by remaining on the spindle, we must suppose that they remain on the spindle and do not fly apart to the edges of the cell for the same reason.

We can test these conclusions by a number of specific observations. Bivalents are formed exceptionally (as in hybrid lilies and grasshoppers) in which only one chiasma is formed instead of three or four, and the centromeres are therefore much farther apart than usual, so that their mutual repulsions become insignificant. They fail to show tension between their centromeres. Such bivalents fail to co-orientate themselves. Again when a bivalent is late in arriving on the plate and cannot twist itself into an axial position in the restricted space left to it on one side of the plate, its unorientated centromeres show no special stretching of the parts of chromosome between them.

Thus repulsions in the spindle are enhanced in an axial direction. Now it is in this direction that the fibrous constituents of the spindle are orientated.[1] This may be shown by the effect of hypertonic solutions on the spindle. It contracts sideways and not lengthways. The enhancement of repulsions therefore is evidently correlated with the distribution of water in the spindle. It works in the direction in which the water is orientated. This orientation takes place in various ways.

The simplest method of origin of the spindle is seen in animals and lower plants where it develops under the influence of particular bodies, the *centrosomes*. These bodies have the permanence, individuality and methods of division of the centromeres, but they lie free in the cytoplasm outside the nucleus and unattached to the chromosomes. One is associated with each nucleus. It divides at telophase, and the daughter halves separate at the end of prophase. A radial orientation of the cytoplasm develops round each, which extends into the nucleus, forming the spindle by union of the two sides.

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[1] Belar, 1929.

In some Protista the centrosomes may develop the spindle inside the nuclear membrane, which breaks down only at anaphase. In others the spindle may develop without any centrosomes either inside or outside the nucleus. The two sides of the spindle are then less convergent and no clear pole can be distinguished. Such is also the position in the higher plants, and here it has often been shown that there are no individual spindle organisers, since single chromosomes lost in the cytoplasm can set up little spindles of their own. This last condition is established in some aberrant plants and regularly in the coccid bugs, where the joint spindle arises from the fusion of separate centromere spindles.[1]

In short the organisation of the spindle shows a greater evolutionary range than that of the chromosomes. Its evolution is probably conditioned by the compartment, cell or nucleus, in which it works. The co-operation of the centrosomes, for example, is dispensed with in the higher plants, where the cell is usually contained within a rigid wall.

As the metaphase plate forms, the spindle widens in the equatorial region both in meiosis and mitosis. When pairing happens to fail at meiosis and the univalents do not congress on the plate, the spindle does not expand in the middle; on the contrary it stretches lengthwise. Evidently the spindle, even when it is formed externally, is liable to modification by the chromosomes. This is shown further by the convergent orientation of multivalents. The co-orientation of centromeres cannot be supposed to be along absolutely predetermined axes or generators of the spindle, since one can repel two others along two convergent axes. We must bear this property of modification in mind when we consider anaphase.

The formation of the metaphase plate shows that the chromosomes, or more particularly their centromeres, are repelled by the centrosomes or the poles. They lie half-way between the centrosomes in mitosis because their repulsion is equal. They are not pushed off the spindle because, as we saw, their repulsion would be lower off the spindle than on it.

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[1] Darlington and Thomas, 1937.

We therefore have the remarkable situation that two repulsion centres at the poles cause an orientation of water in the spindle, and this orientation of water causes an orientation of repulsion centres attached to the chromosomes which in turn modify the orientation of water in the spindle. The means by which water can be orientated is clear. If long chain molecules exist in the cytoplasm and water is attached to them laterally, the orientation of these molecules will cause an orientation of water, and any conditions favouring an orientation of water will favour an orientation of such molecules. Apparently a centre of electrostatic repulsion favours any orientation in its neighbourhood that will increase the effectiveness of its repulsion. Since water has a higher dielectric constant than any other constituent of the cytoplasm an orientation of water will be specially favoured (Fig. 12).

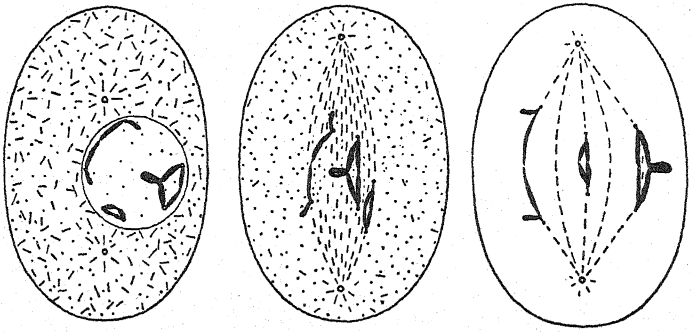

Fig. 12. The relationship of spindle orientation to the co-orientation of bivalents at first metaphase. (After Darlington, 1937 *a*.)

This metaphase system is a system of balanced repulsions. It is ended by the anaphase movement. The chromosomes move apart a short distance under the centric repulsions. These take effect differently in bivalents at meiosis and in unpaired chromosomes at meiosis or mitosis. In bivalents there is no change at the centromeres, which do not divide; metaphase comes too early. The change of equilibrium is brought about by a lapse of chromatid attractions. In unpaired chromosomes the centromeres divide; there is a change of equilibrium owing to four repulsion centres replacing three, and the daughter centromeres move apart. In all cases the change to anaphase is helped by a waning of the repulsion from the poles.

Accidents sometimes happen when the attraction does not lapse quickly enough. In bivalents of a *Chorthippus* hybrid the chromatids are then broken between the centromeres and the first chiasma, and the chromatids may even be broken in mitosis.[1] In univalents other accidents may happen owing to the centromere dividing crosswise instead of lengthwise. Such a fragmentation may take place in *Tulipa* and *Fritillaria* at the second division when a proper division has taken place at the first. Its products survive with terminal centromeres.[2]

As soon as the centromeres move apart the spindle between them changes shape. It stretches, and this stretching is probably in part due to the change of the spindle between them from a centrosome to a centromere spindle, no longer a spindle in shape but a cylinder. It is also probably in part due to the inherent and cumulative stretching of the spindle which occurs throughout its life and leads to fantastic bending and distortion in meiosis where unpaired chromosomes have failed to come on to the plate. Thus the first part of chromosome movement is due to the centromeres pulling; the second part, which inevitably follows, is due to the spindle pushing.

The comparison of mitosis and meiosis, of prophase and metaphase, of normal and abnormal pairing enables us to construct in this way a picture of the successive relationships of cause and effect which make successful nuclear division possible. We see three balanced cycles of activity concerned: chromosome, centromere and centrosome or pole. Each has its own time of division: resting stage, metaphase, and telophase. Each has its own cycle and degree of repulsions. The chromosome cycle is correlated with a cycle of spiralisation of hydration and of staining reactivity, and all three must be correlated by their relationship with changes in the properties of the substrate. Furthermore the contrast between the behaviour of the chromosomes inside this membrane and outside it assures us that the observed fluidity of the nuclear sap is due to the exclusion of spindle-forming materials and must be conditioned by a semi-permeability of the membrane.

Finally we notice that the centromeres of meiotic metaphase bivalents must be less advanced than those of mitotic metaphase chromosomes, for two reasons. They are capable of co-orientation although dicentric chromosomes at mitosis are not. And they are not capable of self-orientation and division unless they are delayed. Apparently the precocity of the prophase in meiosis extends to metaphase and provides a new balance which works satisfactorily by co-orientation replacing division of the centromeres at the later stage, just as pairing replaced division of the chromosomes at the earlier stage.

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[1] Klingstedt, 1938.

[2] Upcott, 1937; Darlington, unpublished.

This analysis of chromosome movements shows that (contrary to previous views) it is not necessary to imagine any change in the kinds of forces acting on chromosomes between prophase and metaphase, or between metaphase and anaphase, or even between mitosis and meiosis. The differences between these different conditions are of degree and not of kind. They depend on the relationships of constant bodies, centromeres and chromosomes, and of substrates which are cyclically changing with a series of correlated effects on the spiralisation of the chromosomes and the repulsion of the centromeres.

Such a constancy was inevitable at some level of analysis. We may therefore look forward to considering (although it is outside our present argument) the relationship between the movements of chromosomes and the molecular structure which they express.

CHAPTER XII

GENOTYPIC CONTROL

THE sizes of chromosomes in any individual are usually constant at all mitoses throughout development. The differences in size shown by the chromosomes of related species can often be accounted for sufficiently by such structural changes as have been described. Sometimes however they cannot. The chromosomes in one genus of flowering plants, *Drosophyllum*, are a thousand times the size of those in the related *Drosera*. Similarly the chromosomes of *Anemone flaccida* are 200 times larger than those of *A. pratensis*. Such changes must be due to a unitary control of the sizes of chromosomes. This control is shown by the behaviour of crosses, mutants and segregates to be genotypic.

Thus in crosses between species with chromosomes of different sizes the chromosomes from one parent are all reduced, from the other increased, in size, e.g. *Crepis neglecta* × *C. capillaris*. *Tradescantia brevicaulis* is a triploid, probably a cross between a diploid species with small chromosomes and a tetraploid with large ones. In a bud sport the chromosomes were one-fifth the size of those of the rest of the plant. Amongst sister seedlings from the same parents in *Lolium perenne* one had chromosomes 20 times larger than another. We must therefore take the chromosomes we see at metaphase as being a measure not of genes but of the aggregation of genes or of their accessory materials. And the degree of aggregation is controlled by the genotype as a whole (Fig. 13).

The uniform diameter of the chromosomes in any one mitosis likewise shows the working of a unitary control, and mutations in this respect also attest its action in many plants and animals. Formerly it was customary to speak of this control and of the changes it brings about as due to the action of the cytoplasm. Undoubtedly the cytoplasm is the vehicle of this genetic action, as indeed it must be of all genetic actions, apart from position effects within nuclei. But there is now no longer any excuse for shirking the inference that all these variations are genotypic and chromosomal in origin. In a word the joint action of the chromosomes constituting the genotype determines the uniform character of their individual behaviour. A single gene may alter the movements of the whole lot.

It is in terms of genotypic control that we must therefore think of the whole range of variations in chromosome behaviour in mitosis and meiosis.

Observations of abnormal mitosis are chiefly restricted to pollen grains, that is to the parasitic generation where unworkable mechanisms are protected from destruction. Here we find mitoses with every kind of time derangement of spindle and chromosomes; semi-meiotic mitoses, variable spiralisation, variable size and orientation of spindle, failure of anaphase.[1] The importance of these observations is in showing the independence of the internal and external parts of the mechanism of nuclear division and their normal co-ordination, which we have already inferred in regard to the theory of meiosis.

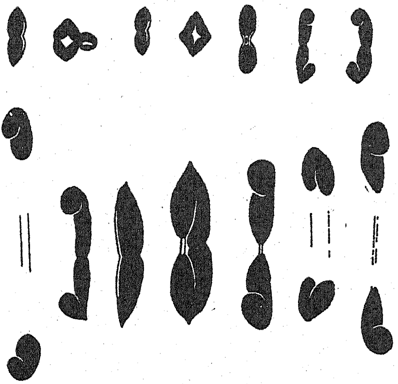

Fig. 13. First metaphase and early anaphase in two sister seedlings of *Lolium perenne* ($n = 7$) to show size difference. × 1700. (Thomas, 1936.)

The most interesting genotypic abnormalities are the modifications of meiosis in the direction of mitosis by a reduction in the precocity of the prophase. The simplest of these modifications is found very generally but in various degrees amongst plants and animals with large chromosomes. It might indeed be regarded as an original property of chromosomes beyond a certain size, the mechanism of meiosis being only afterwards adjusted to allow for the size, for the following reason. The longer the chromosomes the longer it will take them to pair. There is a *time limit* to pairing, depending on the precocity of the prophase. At a critical time unpaired chromosomes divide and then can no longer pair by attraction. The third unpaired chromosome in a triploid is divided at pachytene. Evidently the threshold for division, or more properly reproduction, is, as we might expect, lower in an unpaired chromosome than in a paired one. The attraction for a partner reduces the attraction for substrate materials, which must therefore reach a higher concentration before it results in reproduction. However this may be, the imposition of a time limit restricts the pairing to the regions where it begins; consequently it restricts the crossing-over also, and the location of chiasmata at metaphase (very little movement of chiasmata taking place in these large chromosomes) shows how pairing is initiated in these species. The chiasmata, we find, are *localised* either near the ends (terminally) or near the centromeres (centrically) or near both (Figs. 14, 18).

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[1] Beadle, 1933*b*; Darlington, 1937*a*.

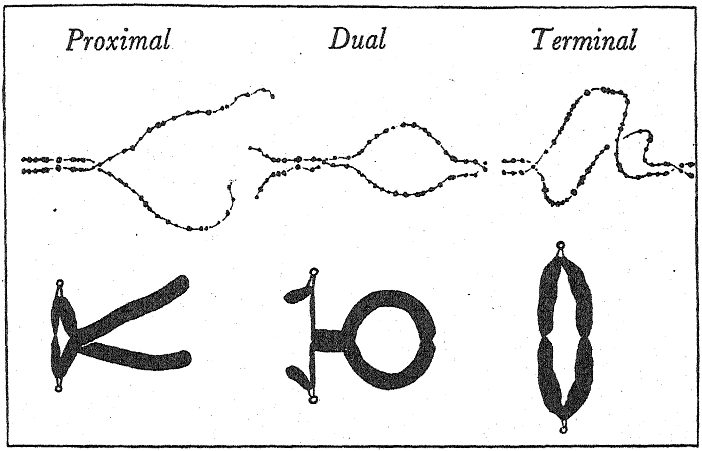

Fig. 14. Three types of localisation of pairing in long chromosomes with little terminalisation. Above, pachytene; below, first metaphase. The centromeres are submedian in the terminal type. Types: *Fritillaria*, *Chrysochraon* and *Tradescantia* (4*x*).

Species of *Fritillaria* show us the meaning of this distinction because they have different chromosomes with centromeres near the ends and near the middles of the chromosomes. In both types chiasmata are localised near the centromeres, never near the ends which are not adjoining a centromere. The grasshopper *Mecostethus* has all its chromosomes with subterminal centromeres and the chiasmata localised near the ends which have the centromeres. These are examples of extreme localisation. Some species of both *Fritillaria* and *Mecostethus* however are intermediate. Chiasmata are occasionally formed at the distal ends of chromosomes as well. Now in species of *Fritillaria* with extreme localisation we find more chiasmata, indicating more pairing, in chromosomes where the centromere is near the end than where it is in the middle. Evidently an end has an inherent advantage in pairing in any organism because it can move freely; the middle parts are tethered; hence the pairing of ends, where localisation is intermediate. This helps us to understand the opposite type of terminal localisation. In the tetraploid species of *Tradescantia*, pairing and chiasma formation are restricted to the ends while the centric regions which are remote from the ends rarely form chiasmata. An intermediate condition is found in another grasshopper *Chrysochraon* where chiasmata at metaphase are all either terminal, or very close to the centromere.

Associated with these cases of localisation characteristic of certain species we often find a reduced spiralisation. The reduced precocity of the prophase is associated with a more mitotic shape of the metaphase chromosomes which even show their nucleolar constrictions as at mitosis. This correlation holds with mutant forms of *Matthiola incana* and *Secale cereale* which have "long" or mitotic chromosomes at meiosis and some reduction in chiasma frequency (Fig. 15). Some more extreme mutants have their chiasma formation and metaphase pairing largely suppressed. In *Zea Mays*[1] and *Crepis capillaris* strains of this kind occur, but these show neither the failure of pachytene nor the reduced metaphase spiralisation that goes with it. It may be that the pachytene pairing seen in these cases to be complete is not true attraction pairing but largely an intermittent torsion pairing of already divided chromosomes. Alternatively it may be that pachytene is normal but that crossing-over is somehow directly suppressed. There is as yet no critical test of these alternative assumptions.

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[1] Beadle, 1933*a*.

The converse inference may be drawn in *Drosophila melanogaster*. A mutant genotype suppresses crossing-over in females. The chromosome behaviour has not been seen, but the progeny show that the suppression of crossing-over entails complete failure of pairing, and frequent unreduced egg cells are formed.

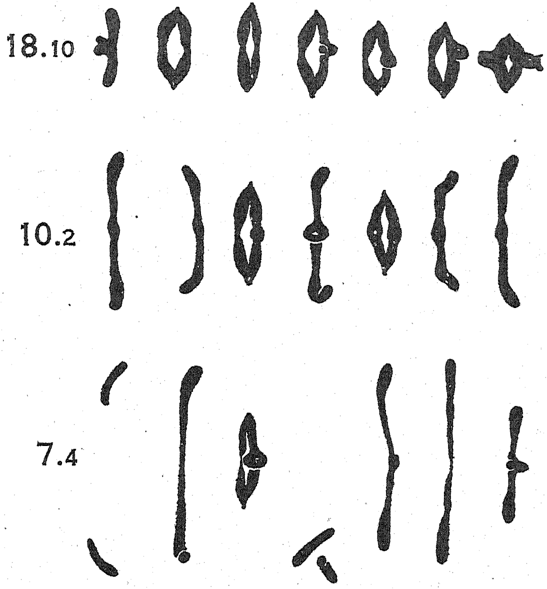

Fig. 15. First metaphase in normal and semi-precocious meiosis in forms of *Secale cereale*. Left: The numbers of total and terminal chiasmata in each cell. Four univalents in the bottom cell. (Lamm, 1936.) Reduced precocity entails reduced pachytene pairing and hence reduced chiasma frequency.

The non-pairing *Zea Mays* reveals a particular property of adaptation. It shows how nicely the organism is adjusted to secure regular pairing with a minimum amount of crossing-over. In the general absence of pairing it was expected that the occasional progeny should show no recombination from crossing-over. But the frequency of crossing-over was found to be normal. What had happened was this. A proportion of pollen mother cells had some pairing—a variable amount; some even had complete pairing. Mutant genotypes are not buffered against environmental variations. Cells which gave progeny were solely those rare ones with ten bivalents. These cells must have had a chiasma frequency between the normal and the minimum compatible with complete pairing. The experiment proves that the normal and the minimum are the same. The same exact adaptation and buffering of the meiotic mechanism is revealed by the variety of disordered types that are produced in the second generation when two differently adjusted species are crossed (Fig. 16).

We thus see that directly or indirectly genotypic conditions may modify the distribution of crossing-over in the chromosomes or may suppress it altogether. And in suppressing it, unless some special secondary mechanism is introduced, they also suppress segregation, reduction and the ordinary course of sexual reproduction. Since all genetic variations are subject to selection these must provide the materials for important changes in the genetic system if such changes happen at any time to have selective value.

Not only the mechanical but also the physiological properties of the genetic system are subject to genotypic control. This is shown in relative sizes of growth of haploids, diploids and polyploids. Where the haploid or polyploid arises from diploid ancestors, through an error in reproduction, it is different from the diploid (smaller or larger). But where it is a regular part of the sexual cycle it can be adjusted to precisely the same size. Haploidy and diploidy then have no differential effect on growth. In some red and brown algae the two phases can have the same type of growth. Similarly in the Hymenoptera the males which are normally haploid need be no smaller than the diploid females. And when a male turns out to be diploid (owing to a breakdown in its system of sex determination) it is no bigger than a haploid. The genes can be adjusted or *compensated* to produce the same effect in double dose as in single dose. The same method is used, as we shall see, to control the action of the genes in a sex chromosome when there are one in one sex and two in the other.[1]

This physiological control evidently works to maintain a uniform action of genes in a changing environment, where such a uniform action is desirable. The genes are buffered against such changes as are likely to upset their co-ordinated action in the system. Single gene mutations represent the minimum change and the minimum unbalance. Buffering by selection of modifying genes is probably responsible for the general dominance of wild-type genes in old established species over their mutant alternatives, most mutants depending on the suppression of an old activity rather than on the invention of a new one.[1]

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[1] Muller, 1932*b*.

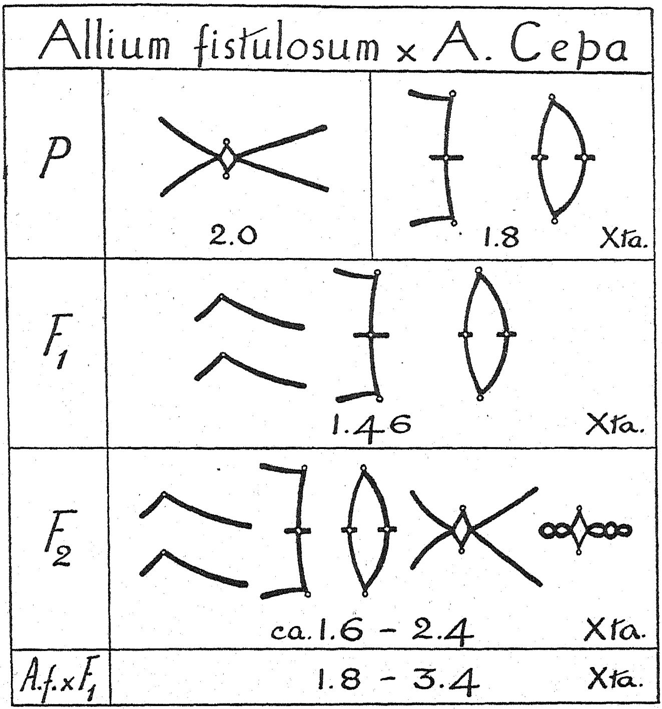

Fig. 16. Chiasma frequency and distribution in two species of *Allium* and in their cross and its derivatives. Numbers are average frequencies for individuals. In the F_2 all types shown may occur in one individual. The occurrence of the last type proves that the two preceding types, occurring in the same nuclei, are due to localisation and not movement. Recombinations in the F_2 prove that the following independent genetic variables are concerned. (i) The time limit, causing variable degree of localisation. (ii) The place of beginning of pairing, proximal or distal. (iii) The regularity of spacing in the nucleus and hence in the place of beginning pairing. (iv) The chiasma frequency per unit of length paired, causing an increase of total frequency in some individuals. There is also evidence of inversion and interchange hybridity in the F_1. (After Levan, 1936; Maeda, 1937.)

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[1] Muller, 1932*b*; Fisher, 1930; Harland, 1936.

There is a third aspect of genotypic control not less fundamental than the others: its effect on mutation rates. Frequency of mutations, as we shall see later, is controlled by the genotype. In view of the enormously different requirements of asexual bacteria without gene recombination, of flies with frequent sexual generations and of trees with vastly infrequent generations, we are bound to expect some degree of adaptation in the genotypically controlled mutation of these forms. We are equally bound to expect, however, that this adaptation will lag behind the changing needs of the organism, particularly when the need is for an increase of mutation. That is in part why we find that trees have lagged behind the rest of flowering plants in evolution.

The various types of genotypic control make it possible for genes to be inherited independently, while the genetic system is selected as an integrated whole. The genes are like the members of a legislature in being subject as individuals to the laws they enact as a body. And it is through this subjection that the adaptation and evolution of the genetic system has been possible.

CHAPTER XIII

THE MECHANISM OF CROSSING-OVER

STRUCTURAL changes in the chromosomes take place by the breakage of the threads in one or more places. This is followed by reunion of the broken ends in new combinations. Such a reunion does not always follow, but it is always necessary for keeping the whole complement of genes intact and therefore for the survival of a balanced cell. Crossing-over likewise depends on breakage and reunion, but it occurs regularly at the pachytene stage of meiosis and at no other stage. Moreover, it consists in an exact recombination of the parts of chromosomes, which are closely paired at this stage and no other. We ought therefore to be in a position to say what it is in the mechanical conditions of the paired chromosomes that allows of this regular consequence of their association. What are these conditions?

During pachytene the paired chromosomes develop relational coiling. How they do this may best be seen by placing two twisted woollen threads close together. When they are released they untwist themselves individually and in doing so, since they stick together laterally, they twist round one another. They are, however, now found to be only half untwisted. Their *internal* torsion has come into equilibrium with an equal and opposite *relational* torsion. This equilibrium is the basis of all spinning operations. The internal torsion of the wool corresponds to a strain set up in the molecular spiral of the chromosome. The same change under other conditions produces an internal instead of a relational coil.

The pachytene equilibrium must be of the same kind essentially as the spinning equilibrium, since the forces responsible for both are known on other grounds and are analogous. The wool threads stick together by friction, the chromosomes by specific attraction. Their not slipping round one another shows that this attraction is specific in direction as well as in choice of partner. The wool and the chromosomes coil equally because they resist torsion. They both have longitudinal cohesion. Both these properties are likewise necessary if the chromosome is to reproduce to give a regular and coherent daughter thread. From which it follows that when the two chromosomes are internally twisted at the end of pachytene they will each divide to give two daughter threads coiled round one another. And this coiling will presumably be in the opposite direction to that of the relational coiling between chromosomes (Fig. 17).

The proportion of the internal torsion which is released to give relational coiling varies in the wool model according to the amount of torsion. So also it must be with the chromosomes. Not only this. The size and strength of the threads, and thus any external conditions affecting these properties, will modify the pachytene equilibrium. One special circumstance must be remembered. Where the ends of the chromosomes, or of certain segments, are fixed, no relational coiling at all will be developed between chromosomes. This will necessarily occur within inversion loops. It is also likely to occur when the pachytene stage is short and equilibrium is never reached. The state of strain under these conditions will not be diminished. Rather will it be increased. And the conditions of crossing-over will be the same. The difference will be in the result. At diplotene more chromatid coiling and less chromosome coiling will be seen. How far the variations actually found at diplotene depend on such differences in the normal pachytene equilibrium and how far on partial failure of pairing at pachytene we do not yet know.

Such must be the varying conditions at the end of pachytene. What relation have they to the action of crossing-over? It will be recalled that in *Fritillaria* the pachytene pairing is often confined to two regions, centric and terminal, with an unpaired region in between. This type of association is of critical importance, for in the unpaired middle region the same torsion arises and, since the two ends are held together in the paired regions on either side of it, the same coiling necessarily occurs, as in these paired regions. No crossing-over can take place in an unpaired region however. What do we find at diplotene? In the paired regions chiasmata are formed and no coiling is left, while between them in the formerly unpaired regions coiling still survives. Apparently therefore chiasmata replace coiling in the paired parts at the end of pachytene. They must then be determined by the coiling strain which they themselves remove (Fig. 18).

In other organisms such as a garden tulip, a lily or the grasshopper *Chorthippus*, a small proportion of the pachytene coiling

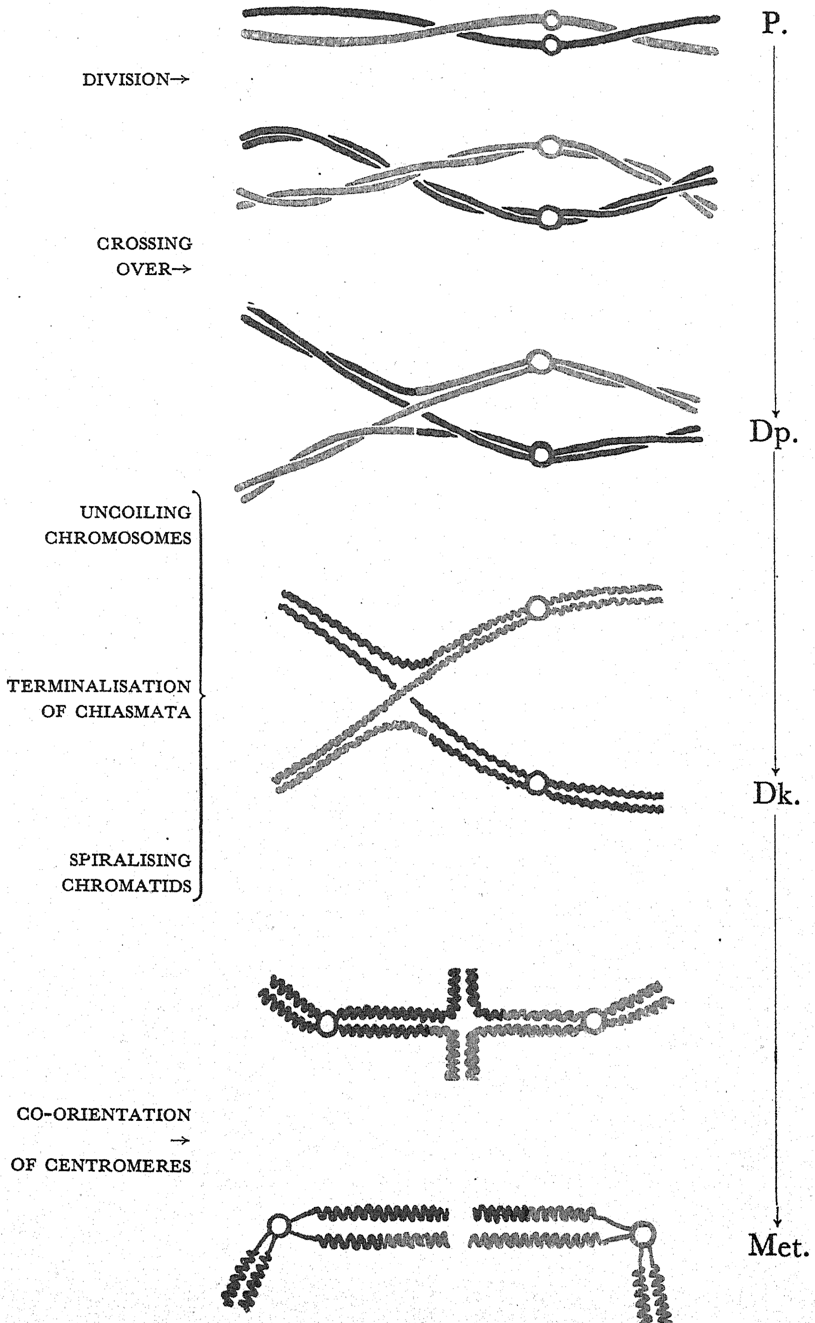
P.
DIVISION→
CROSSING OVER→
Dp.
UNCOILING CHROMOSOMES
TERMINALISATION OF CHIASMATA
SPIRALISING CHROMATIDS
Dk.
CO-ORIENTATION → OF CENTROMERES
Met.

Fig. 17. The mechanical and genetical relationships of paired chromosomes during the prophase of meiosis.

still survives at the earliest diplotene stage, although pairing has presumably been complete at pachytene. At diplotene, relational coiling can then be seen in three distinct forms. There is a coiling of the chromosomes round one another between chiasmata, a coiling of the chromatids of each chromosome also between chiasmata, and finally a coiling, or rather a mere crossing, of two of the four chromatids at each chiasma which is a relic of the earlier chromosome coiling (Fig. 3*a*). All these types of coiling disappear in free arms before diakinesis. In closed loops the other two kinds are both translated into chromatid coiling: each loop flattens in one plane and successive loops come to lie at right angles, making each chiasma symmetrical.

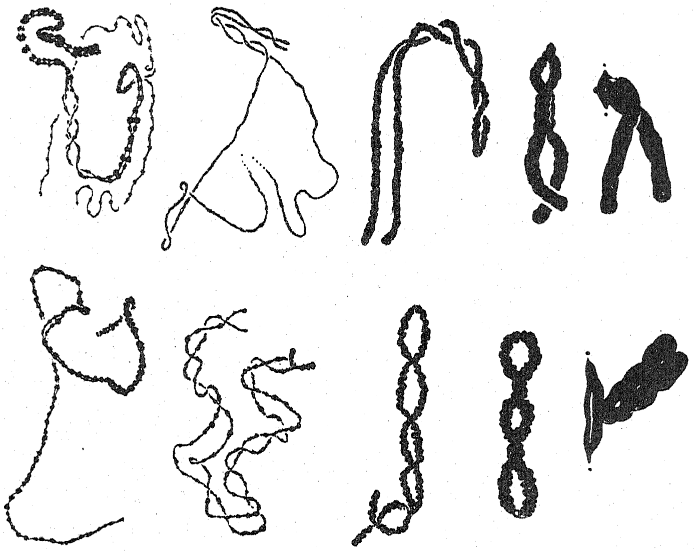

Fig. 18. Pachytene to first metaphase in *Fritillaria*. Above, in a species with moderate proximal localisation giving intermittent pachytene pairing and consequent survival of relational coiling. Below, in a species with complete pachytene pairing and consequent replacement of relational coiling by chiasma formation throughout the length of the chromosomes. Subterminal centromeres in both bivalents. (After Darlington.)

It remains to explain how the strain of relational coiling can determine crossing-over when the pachytene equilibrium is brought to an end. It will be seen at once that this situation is unique in the history of the nucleus. Two chromosomes in a state of strain are split into four chromatids. At the same time the attraction between the chromosomes lapses. Each chromosome has to support separately its internal strain. Equilibrium can only be re-established by the abolition of all relational coiling, but as observations of the diplotene stage show us, even the coiling of free arms does not disappear for some time. There is a lag in the adjustment of external form to internal stresses, the same hysteresis indeed which we noted in regard to relic coiling. It is this combination of a sudden strain with a delayed adjustment in a system, the elements of which have been weakened by division, that must be supposed to lead to a breakage of chromatids.

The diplotene change begins near the centromere in *Fritillaria.* Elsewhere it may begin near the ends. It is not likely to be simultaneous throughout each chromosome. Nor can the breakage of two chromatids at one chiasma be simultaneous. When a chromatid breaks between two genes the strain on its partner will be released by the release of their mutual coiling. The two broken ends will revolve round their unbroken sister in opposite directions. At the same time the strain will be increased on the chromatids of the partner chromosome, for the coiling of the two chromosomes has been in equilibrium with that within each. When the strain on one is removed by breakage, that on the other is increased. On account of the specificity of the attractions between genes, this increase of strain will be greatest at the point immediately opposite the first break. The first break will therefore immediately determine a corresponding one in a chromatid of the partner chromosome. Its two broken ends will uncoil and in doing so will meet the ends of the others before they meet one another again. They will rejoin just as the broken ends do when structural changes occur.

Now since the ends of the chromosomes are free and the centromeres are single and show no specific attractions, both the ends and the centromeres are likely to be points of zero torsion. Only at a certain distance from them will the critical strain for crossing-over develop. Crossing-over will be suppressed in certain regions.[1] Similarly when crossing-over has occurred, reducing the strain in its neighbourhood, the chance of another cross-over near the first will be reduced. In fact crossing-over will be impossible within a certain distance, which will depend on the amount of coiling that has been undone by the crossing-over. Hence if the distributions of cross-overs are measured from the centromere we should expect zones of high and low crossing-over to be spread along the chromosome, gradually disappearing beyond the second or third chiasma. This is approximately what is observed in species of *Drosophila*. Especially it must be noticed that very close to the centromere there is no crossing-over. There will also be *interference* between successive cross-overs. Such interference has been measured from linkage by Muller and from the frequency distributions of chiasmata by Haldane. The frequency of double crossings-over within short distances is less than randomness requires. The curve of chiasma frequency per bivalent is narrower than a Poisson distribution will allow. Finally there should be no interference across the centromere: this is shown to be true both from chiasmata and from linkage experiments.[1]

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[1] Mather, 1938.

If these views are correct and repulsion is the agent both of crossing-over and chiasma formation we may say not that crossing-over determines chiasma formation but that they are indeed one and the same thing.

We are only at the beginning of our understanding of crossing-over. In special circumstances it has special properties. Some of these will be dealt with later. But the first questions that may be asked about the mechanism of crossing-over have now been answered in terms of the behaviour of the chromosomes known at other stages of their history.

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[1] Mather, 1938; Bennett, 1938.

CHAPTER XIV

THE BIOLOGY OF RECOMBINATION

THE ordinary course of meiosis shows us the two primary functions of crossing-over. It determines the recombination of the parts of chromosomes. It permits the pairing, segregation and reduction of chromosomes and hence secures the essential conditions of sexual reproduction. The importance of sexual reproduction, as Weismann pointed out, lies in its effecting a recombination of the parts of the hereditary materials which exposes them to the most efficient natural selection. This recombination we now see is more profound than Weismann imagined. It extends beyond the chromosomes to the genes. The number of units capable of recombination is not five or even fifty, but five thousand or fifty thousand. These units are units of heredity by virtue of crossing-over. If crossing-over ceases to occur they cease to be units.

It is clear that for any particular inter-mating group there must at any particular time be an optimum amount of recombination and therefore an optimum number of chromosomes and an optimum amount of crossing-over between them. We might consider these together by taking the sum of the haploid number of chromosomes and of the average chiasma frequency of all the chromosomes in a meiotic cell as a *recombination index*. Too high an index would be deleterious by breaking up advantageous combinations; too low an index would never achieve the most advantageous combinations. One would suppose on grounds of recombination alone that one chromosome would always be better than several, since genes in different chromosomes can never be kept together. But in fact genes at opposite ends of a long chromosome can also never be kept together, and as a consideration of the mechanics both of mitosis and meiosis shows, a single long chromosome, or more especially a single centromere, will not give the easiest separation. The only organism with a single pair of chromosomes, the threadworm *Ascaris*, seems to have several co-ordinated centromeres lying close together in them[1].

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[1] White, 1937.

The optimum recombination index will depend on the number and concentration of gene variations to be recombined within the group, the size of the group and its freedom of mating. Have we any reason to suppose that such an optimum—whatever it may be—is generally attained? We certainly have not. Chiasma frequency as a rule has to meet the requirements of regular pairing and reduction before it can meet those of crossing-over. Chromosome number is often one of the most conservative properties of the genetic system. The same number is found constantly in large sections of the Orthoptera, the Gramineae and the Rosaceae. On the other hand, unrelated species having similar genetic systems in other respects have entirely different numbers. It should moreover be easier to increase the chromosome number than to reduce it. Both mean a change in the number of centromeres by their loss or reduplication together with that of the adjoining parts of the chromosome, and unless these parts are inert their reduplication will have a less dangerous effect on the balance of the organism than their loss. Great variability of the chromosome numbers of a group, due to structural change, is therefore an indication that the proximal parts of the chromosomes are inert. In a word it seems that increase of chromosome number is an evolutionary step that often cannot be retraced. It offers immediate advantages at the expense of ultimate survival (Fig. 19).

Chiasma frequency, on the other hand, is sometimes readily variable. Within the species *Fritillaria imperialis* clones exist with an average chiasma frequency per bivalent differing as much as 2·6 and 5·0. In general however (as we saw in *Zea*) the chiasma frequency is the minimum compatible with regular pairing in the shorter members of the complement; the short bivalents of *Chorthippus* for example have one usually, and rarely two chiasmata (Fig. 3*a*).

Supernumerary chromosomes which arise in many species from time to time do not always form a chiasma when they are smaller than any of the rest of the complement. Chiasma frequency is proportional to length. This shows that the species is adapted to have regular chiasma formation and metaphase pairing for its ordinary complement and is not adapted to provide for shorter members. Statistical comparison in *Secale* shows that the ordinary bivalents have 2·42 chiasmata on the average, while an extra short pair (one-third their length) has 0·83 chiasmata and therefore sometimes fails to pair. The same lack of pairing is found in small extra chromosomes in *Fritillaria*, *Matthiola* and *Solanum*.

The condition in species with a wide range of size in their normal complement is radically different. The small chromosomes regularly pair with a single chiasma, the longer ones have several chiasmata but their frequency is usually less than proportional to their length frequency. In *Chorthippus*, where the long chromosomes are more than five times as long as the short ones, they have only 3·3 chiasmata on the average. The same discrepancy is found in many Liliaceae. Evidently these species are adapted so as to economise in the number of chiasmata formed. Lower crossing-over has, as we might expect, a selective value.[1]

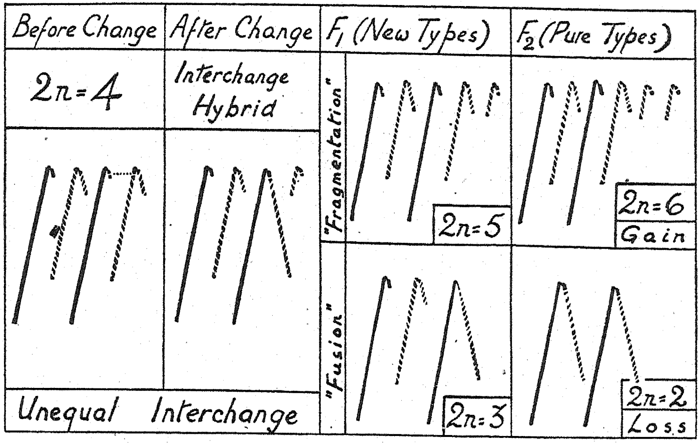

Fig. 19. Diagram showing how two pairs of chromosomes can become one or three in evolution following interchange in a diploid. The first requires loss of a part of a chromosome near its centromere and this part must therefore be inert. The second requires gain of a similar part which need not be inert. (After Darlington, 1937 *a*.)

The mechanism which equalises the number of chiasmata formed amongst chromosomes of different lengths is probably of various kinds. There is evidence of two methods that might be effective. It might take effect by the interference of the centromere with crossing-over near it being less than that of crossing-over itself.[2] Or it might be due to the pachytene pairing of the chromosomes beginning simultaneously and the last parts of the

[1] Fisher, 1929.

[2] Mather, 1938.

long ones to pair being already partly uncoiled when they pair, so that the coiling strain developed in them will not be proportional to their length. In *Mecostethus* it is in fact achieved by localisation of pairing.

Another means by which crossing-over is reduced in the system is its abolition in one sex, as in the male *Drosophila* and *Callimantis*[1]. The male genotype determines a special type of meiosis in which crossing-over and chiasma formation are dispensed with, and the chromosomes pair by an extension of the usual primary attraction from two threads to four. This device has the effect of reducing the average recombination index of the species. Now chiasmata are formed at meiosis (in one sex or both) in all sexually reproducing species. *Drosophila* shows that the original conditions of meiosis can be removed. It is not now chiasmata which are necessary for the chromosome pairing in the individual, but crossing-over which is advantageous for gene recombination in the species.

Both in chromosome number and in chiasma frequency, however, we must expect that species are very imperfectly adapted to their needs of recombination. The lag in adjustment will be even greater than in other properties of the genetic system because their adaptation is a compromise. Both of them have other effects unrelated to their function of recombination and these effects will react on the species more rapidly than errors of recombination. Let us now consider some of these.

Simple inversion of a segment of chromosome, unless it produces a position effect, has no significance apart from crossing-over in the hybrid. When single crossing-over occurs between the dislocated segments in an inversion hybrid, and the dicentric chromatid breaks into two, two new chromatids are formed. They are deficient for the end segment, and one of them may have a reduplication of a proximal segment if the chromatid breaks unequally. Such chromosomes are not likely to survive unless they are supernumerary to the ordinary haploid set. They should be particularly important therefore in polyploids, and in fact they arise frequently owing to special circumstances in all triploids and in many tetraploids.

In triploids there is the equivalent of a whole extra set made up of parts of chromosomes unprovided with partners at pachytene. Short segments, such as we saw were frequently repeated within the

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[1] White, 1938.

haploid set, are thus in a position to pair with one another as they never could in a diploid. We therefore often find pairing within this third set. A triploid *Triticum* or *Fragaria* with 21 chromosomes, instead of forming a maximum of seven associations (trivalents or bivalents and univalents), may form eight or nine pairs at meiosis. Some of these extra pairings are due to interchange hybridity. Others are due to reduplications. Some of these again are between inverted segments, some of them between straight segments; even these will of course give rise to new chromosome types, longer or shorter than the original ones and with a different linear order of genes. Triploids therefore in *Solanum* and *Tradescantia* and elsewhere constantly give new chromosome types in their progeny. These are usually small chromosomes, and probably many supernumerary fragments arise in this way.

In new allopolyploids where the different sets, as in *Primula kewensis*, are imperfectly differentiated, chromosomes from different sets occasionally pair and cross over. Sometimes the result is merely a recombination of genes. Frequently however a structural rearrangement takes place, owing to the chromosomes which have crossed over being structurally different. Such changes have often been found in hexaploid wheats and oats. They give rise to important mutants and demand the constant selection of the varieties in which they occur.

Such changes are *secondary structural changes*, and they must be clearly distinguished from primary structural changes of which they are products. Primary changes occur at all stages of development equally in pure and hybrid organisms. Secondary changes occur only at meiosis in organisms which in a broad sense are hybrids—structural or numerical. They occur only through crossing-over between differently placed segments and are therefore liable to be of particular types, each occurring with a particular frequency in a given hybrid. Formerly their effects, like those of primary changes, were ascribed to undefined mutations.

The effects of structural hybridity on crossing-over are no less important than the effects of crossing-over on the progeny of the hybrid. The diploid progeny in which secondary structural changes have occurred usually die, so that crossing-over is, as we have seen, effectively suppressed between the segments in which it will give rise to such changes—within inversions and proximal to interchanges. Recombination is stopped, and in special cases we shall see what effect this may have. The same condition however applies in general to all chromosomes near their centromeres and perhaps also near their ends. We find in fact that near the centromeres of all the chromosomes in *Drosophila* the genes have become inert. It seems that they have mutated to inertness, and selection, with its efficiency impaired in this region by the absence of crossing-over and recombination, has failed to weed them out.

In this light the extreme localisation of crossing-over must have an important effect on the genetic structure of the species. What this effect is we shall see most clearly from the behaviour and evolution of permanent hybrids.

CHAPTER XV

THE PURSUIT OF HYBRIDITY

THE efficiency of natural selection depends on the availability and potential permanence of the largest possible number of combinations of hereditary differences. These properties depend in turn on crossing-over and hybridity. We have seen that crossing-over is regulated and has a certain optimum value which may or may not be attained. Let us now examine the regulation of hybridity.

The first factor determining hybridity is obviously variation, for if there is no change in the genes and the chromosomes there can be no hybridity. We find that both intragenic and intergenic mutation are controlled, at least within certain limits. A gene in one species of *Gossypium* when transferred to another species by crossing has a higher mutation rate.[1] The particular unstable genes whose frequent mutation is responsible for white flowered plants becoming flaked with colour are always found to vary in frequency of mutation subject to varying genotypes. And they vary also in the time and place of most frequent mutation. The same is true of structural changes. In *Zea* a particular gene mutation ("sticky") causes an enhanced rate of structural change. We must suppose therefore that particular species have genotypic properties in this respect more or less adapted to their needs, although no doubt lagging behind these needs as the genetic system changes.

The second factor of importance in determining hybridity will be the system of mating, which in turn will depend on two independently variable conditions: the size of the endogamous group, the continually varying collection of individuals amongst which mating can take place, and the biological and spatial freedom of this mating.

The size of the endogamous group may be limited by factors of entirely different kinds. On the one hand geographical isolation may separate two parts of a species which would otherwise be capable of crossing freely. And the means by which geographical isolation will arise depend in turn on *genetic mobility*, that is, on the individual movements or local conservatism of an animal species, and on the pollen or seed distribution in a plant species. On the other hand, a slight differentiation of sexual habits or time of flowering, or a few structural changes in the chromosomes, or a gene mutation for cross-sterility, or co-ordinated change in the rate of growth of pollen and in the length of the style may any of them establish a *genetic isolation* which will limit the endogamous group to a part of the morphologically homogeneous group. This genetic isolation may occur independently of geographical isolation, or may follow it. It will lead to all degrees of cross-fertility within the endogamous group and therefore very often to uncertain boundaries between endogamous groups.[1]

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[1] Harland, 1936; Sturtevant, 1937; Rhoades, 1938.

Within the endogamous group the freedom of mating will largely depend on the restrictions on self-fertilisation. Species like *Pisum sativum*, in which self-fertilisation regularly occurs, are uncommon amongst the flowering plants where an enormous number of devices are known for promoting cross-pollination. The morphological devices were explored in great detail by Sprengel and Darwin; the genetic devices have also long been known but only recently understood.

The most obvious genetic device preventing self-fertilisation is the self-sterility gene system.[2] This system is found in its simplest form in fungi where two haploid nuclei will fuse only if they differ in respect of a particular gene or genes. In flowering plants the case is similar: the pollen of a self-sterile plant will not fertilise the same plant or any other plant having a particular gene in the same state as itself. The gene concerned exists in the species in a multiple series of states which may be called S_1, S_2, S_3 and so on. S_1 pollen will not grow on an S_1S_2 style or an S_1S_3 style, only on one, like S_2S_3, which has no S_1 gene. Hence self-fertilisation cannot occur and pure S_1S_1 individuals cannot be produced. A majority of diploid species of flowering plants probably have a differential gene system of self-sterility in some stage of development from a sporadic origin to a universal distribution.

The physiological mechanism may vary. Sometimes the pollen will germinate but dies in the style. Sometimes it will enter the ovule but dies without procuring fertilisation.[3] However they work, these contraceptive genes prevent self-fertilisation and also crossing with other individuals having the same gene. They will not however ensure any cumulative hybridity except in the parts of the chromosome so close to the S gene that very little crossing-over takes place with it.

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[1] Darlington, 1939.

[2] East, 1929.

[3] Sears, 1937: Crane and Lawrence, 1938.

The combination of change, crossing and selective elimination in any stable endogamous group will work together to produce a certain *hybridity equilibrium*. Through their effect on this equilibrium they will react on the rest of the genetic system of the species. The equilibrium may be measured in breeding experiments by the vigour and variety of the progeny from self-fertilisation or inbreeding. At meiosis it may be measured most readily by the frequency of bridges produced by inversion crossing-over.[1]

All sexual reproduction entails inbreeding simply because all endogamous groups are limited by genetic isolation. But we can conveniently contrast the extremes of self-fertilisation and the widest crossing permitted by this limitation.

The effects of self-fertilisation or close inbreeding and cross-fertilisation with remote relatives are markedly different in a diploid species which is normally cross-fertilised. The one reduces the hybridity below the usual level, the other raises it. The one produces offspring of reduced vigour, the other of increased vigour. This property of increased vigour in crosses is known as *heterosis*. It is supposed to be due to the recessiveness of deleterious mutations in respect of some of which each of the parents is pure. Such crosses may be represented as $AAbb \times aaBB$ where both a and b are deleterious. The fact that such deleterious genes are present is due to their general protection from elimination by constant cross-fertilisation. The fact that a wide cross will suppress some that have been showing with the ordinary system of cross-fertilisation shows that elimination of poorer growing individuals has not been rigorous enough for the previous size of the endogamous group. In a word the genetic properties of a group are conditioned by its mating system. Self-fertilisation is not deleterious in a group which has been constantly self-fertilised in the past.

A regularly cross-fertilised group must be entirely upset by allopolyploidy for three reasons. The allopolyploid is a permanent hybrid whose recessive gene mutations cannot segregate when it is self-fertilised. If its diploid parents have a self-sterility system this system will not necessarily work in the new polyploid.[1] Diploid hyacinths are self-sterile, triploids are not. The new polyploid is in any case an endogamous group by itself—the only member of a new species. And finally, as we saw, its method of variation is enlarged by a secondary segregation of ancestral differences. All these conditions are likely to change the character of the genetic system when a new polyploid species is formed. Later when such a polyploid by gradual differentiation of its sets becomes a functional diploid (if it was not so at first), in its general heredity, it will no doubt also become like its diploid ancestors in its mating system. Polyploidy secures hybridity by an irreversible change which nevertheless leaves the species with a long lease of life. We must now consider a more meretricious way of attaining the same end.

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[1] Darlington, 1937*b*.

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[1] Cf. Lawrence, 1931*a*.

CHAPTER XVI

THE PERMANENT HYBRID

THERE are two common conditions in which an inversion, or at least a small inversion, can exist in a species. The first is that in which it is most likely to begin, the condition of free combination between the original and the changed structural types; here pure original, pure changed and hybrid individuals will exist side by side in equilibrium and freely intercross. Such a condition of inversions is found in *Campanula persicifolia*, but equilibrium has not been reached throughout the population of this widely distributed species. Crosses between plants from different regions are in general more hybrid than the wild plants drawn from any one region. Evidently new inversions are continually spreading in the species. This stage of development may be described as the stage of the *floating* inversion.[1] The second stage is that where an inversion becomes fixed in a given part of the species, a geographical or an ecological race. This stage is reached in *Drosophila pseudo-obscura*.[2] Chromosome differences between different species of *Drosophila* or *Lilium* are found to consist largely in inversions such as those which are here found developing and becoming fixed within species. Evidently they have arisen in the same way. The question therefore arises as to why an inversion should become characteristic of a particular race having particular genetic properties which are not implied by the inversion itself. We find the answer in the discovery that the characteristic groups of differences between species or races are often found to be closely linked or even inherited as a single unit. In the case of the speltoid and fatuoid complexes which distinguish important ancestral groups in wheat and oats it seems that inversions are what maintain this unity. They do so by suppressing crossing-over between the group of gene differences which are associated in the complexes. Inversions isolate segments of chromosomes just as seas and deserts isolate segments of a species. We can have an endogamy of chromosomes as much as an endogamy of populations.

Inversions may promote discontinuity within a species in two ways, gradually and suddenly. Small inversions will largely inhibit crossing-over, and floating in the species will survive if they happen to pick up a useful combination of genes. They will act as a brake on recombination amongst these genes. Large inversions, like translocations of any size, will establish discontinuity by making the hybrid infertile through too much crossing-over taking place within them. They will isolate, not the chromosomes, but the organisms, and in consequence are less likely to occur except in a largely self-fertilised species.[1] They seem accordingly to be of less importance in nature. If inversions have acted as crossing-over suppressors and not as sterilisers we should find that short inversions are most frequent and that inversions including the centromere are absent. We should also find that inversions are disproportionately frequent in the longer chromosomes which have a wide enough margin of chiasma frequency to ensure regular pairing in the inversion hybrid. This seems to be true of races of *D. pseudo-obscura.*

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[1] Darlington and Gairdner, 1937.

[2] Dobzhansky and Sturtevant, 1938.

The origin and distribution of interchanges depends not only on whether the species is normally self- or cross-fertilised, and on the size of the interchange, but also on the properties of chiasma movement of the species. If chiasmata remain interstitial as in *Zea* and *Pisum* the associations of four produced in the hybrid are, half of them, parallel in co-orientation and give inviable gametes. If the interchange hybrid is sterile then interchange, like a large inversion, will cause immediate fission in the species. This has probably happened in *Pisum.*

If chiasmata are terminalised, a higher proportion of regular gametes are produced and interchanges large enough to form chiasmata can float in a cross-fertilised species as they probably do in *Campanula persicifolia.* A later stage of this is found in *Datura Stramonium,* where interchanges have been fixed in local races some of which are pure for particular types of interchange.

Interchange has however given results of an entirely different character in certain species of flowering plants. In these species interchange hybrids breed true. In fact the whole species consists of one type, hybrid for a particular interchange or combination of interchanges. How did such a species arise? An interchange floating in a species widely cross-fertilised like *Campanula persicifolia* will always be hybrid at first and will have crossing-over

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[1] Darlington, 1939.

reduced in its proximal segment, as we saw earlier. After a certain period of sheltering in this way it will be impossible for it to exist in the pure condition. If however the hybrid is favoured by heterosis the interchange will spread in the species and interchange hybrids will increase in gene hybridity as time goes on.

In a word, the course of evolution from the floating to the fixed stage can be diverted if the selection pressure in favour of hybridity is strong enough.

Once established, these species with rings of four chromosomes have gone further. In *Oenothera* and elsewhere, more interchanges have increased the size of the ring to include six, eight, ten and finally all fourteen chromosomes. (When 13 of the 14 pairs of distal segments form chiasmata, a chain is produced like that in Fig. 20.) The advantage of the hybridity conferred by a ring of four will of course be increased by each increase in size. It might be thought that irregularities in the distribution of the ring at meiosis would upset the system by increasing sterility, and this undoubtedly restricts the occurrence of ring-forming hybrids to certain groups. Owing perhaps to a happy adjustment of the sizes of the chromosomes and spindle, co-orientation is usually convergent and a majority of the gametes formed even by the largest ring in *Oenothera* are usually regular and viable.

In the ring of fourteen there will be, not only two pairs of interstitial segments in which crossing-over is reduced, but five pairs of *differential segments* in which it is suppressed (*x* in Fig. 9 (iii)). The homologous segments will change independently owing to their being genetically isolated. They will therefore diverge in evolution. The interchange hybrid will become a gene hybrid and the two types of gamete which it produces will come to differ as much as those of two distinct species. Each chromosome will have a terminal pairing segment which will exactly correspond to a pairing segment in a chromosome of the other gametic type, or *complex* as it is called. And proximally each chromosome will have a differential segment which does not normally pair at pachytene or cross over with any homologous segment in the chromosomes of the opposite complex. It is within these differential segments that the genetic differences between the complexes have accumulated and persisted.

In the simplest case each complex hybrid species produces two kinds of pollen grains and two kinds of egg cells. Hence when two different species are crossed four different kinds of hybrid can be produced (as *Oe. Lamarckiana* × *Oe. strigosa*), and each of these will have its own particular properties of ring-formation as well as its own recognisable morphological type. Usually one or two of these fail to live. Similarly when a complex hybrid species is crossed with a non-hybrid species (for a few such still exist) two types of crossed offspring appear. Thus *Oe. Hookeri*, 7 (2), × *Oe. Lamarckiana*, (12) + (2), gives two hybrids, one having the *gaudens* com-

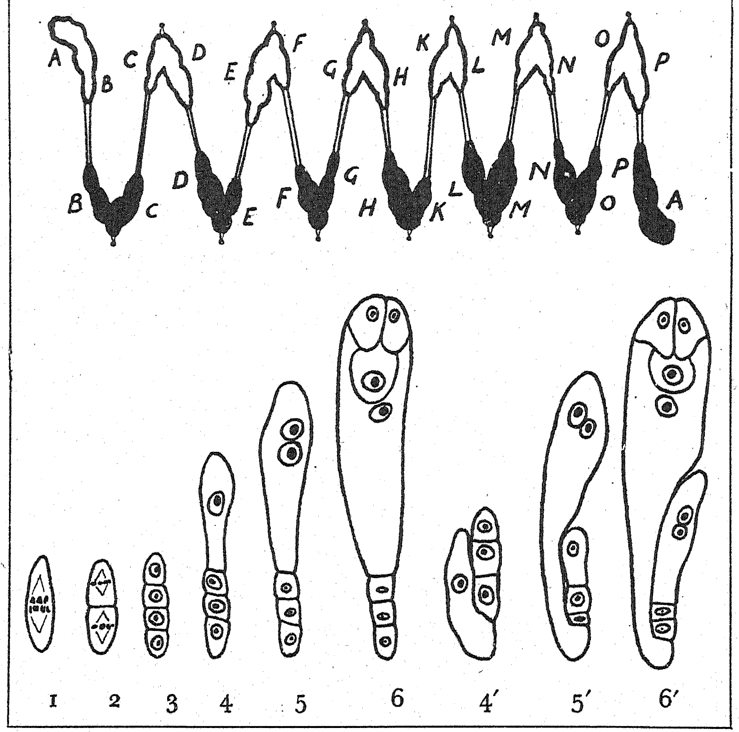

Fig. 20. Above, the regularly convergent arrangement of a chain at first metaphase in a species of *Oenothera* hybrid for six interchanges. Note that a complete set of the labelled pairing segments passes to each pole. Cf. Fig. 9. (After Darlington, 1932 *b*.) Below, the two possible series of events following meiosis in the embryo-sac mother cell of a hybrid species of *Oenothera* according to which cell receives the female-competent complex at the first division. (After Renner, 1921.)

plex of *Lamarckiana* with (10) + 2 (2), the other having its *velans* complex with 2 (4) + 3 (2).

A special situation which we may regard as the most highly developed is found in *Oe. muricata* (14). This species produces pollen grains and potential embryo-sacs with its two complexes *curvans* and *rigens*. But only the *curvans* pollen and the *rigens* embryo-sacs function. The *rigens* pollen grains die; and on the female side a special device is found. The embryo-sac mother cell, as is usual, forms a row of four cells; and when the end cell of the four, which should from its position grow and divide to give the egg cell, happens to have the *curvans* complex it hardly ever grows. It is pushed out of its place by the growth of the cell at the other end, which of course is *rigens* (Fig. 20). This is a specially straightforward example of the cell-struggle and of the natural selection which results from it. The species therefore yields pollen grains entirely of one type, and egg cells entirely of the other. The loss due to the formation of pure zygotes which would die is eliminated. This difference on the male and female sides shows itself in that reciprocal crosses with other species are entirely different. When *Oe. muricata* is the egg parent the crosses are nearly all *rigens* hybrids, when it is the pollen parent the crosses are all *curvans* hybrids. These two kinds of hybrid can always be distinguished, both by their external form and by their associations of chromosomes at meiosis. Such a complementary gametic adaptation clearly makes for economy in reproduction and is due to genetic change during or since the development of the complexes. The genetic action of each complex, it will be noticed, takes place as soon as the genetic character of the cells is established by segregation at meiosis.

As we saw earlier, crossing-over can take place between the differential segments of the chromosomes whose ends are not homologous. But it is exceptional. When it happens, there is a reverse interchange and the two whole complexes in effect cross over.[1] Gametes are produced, half of one complex and half of the other. Combining with normal gametes, wholly of one complex or the other, a new type of zygote is produced which is hybrid for half of its chromosomes, pure for the other half. Such plants are known as *half-mutants* and can themselves yield entirely pure offspring, half pure for one complex, half for the other. These are known as full mutants. Thus *Oe. Lamarckiana* gives 0·1 % of seedlings of a type called *Oe. rubrinervis*, with (6) and 4(2), which itself yields a 1 : 2 : 1 ratio of non-viable seed, the *rubrinervis* type, and the full mutant, *Oe. deserens* 7(2).

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[1] Sweet, 1937.

Full mutants could not arise directly. They show that a workable combination can be made very simply from materials which, as they exist, are in an unworkable combination. They show that recombinations of materials, especially translocations from one complex to the other, rather than specific intragenic mutations are responsible for the unworkable character of each complex alone. And finally they show that "mutation" in *Oenothera* is due to segregation following exceptional crossing-over in a hybrid.

Probably a hundred or two species of *Oenothera* have a complex hybrid structure, and a few species in other genera—*Briza media* (4)+5(2) and *Hypericum punctatum* (16). From crossing varieties with different floating interchanges in *Campanula persicifolia* ($2n=16$), plants with a ring of twelve have been synthesised. only two pairs of chromosomes being left out. Some of these artificial hybrids give an approximately Mendelian segregation in their progeny while others breed true with occasional mutation like the natural species of *Oenothera*.

Complex hybrid species have gained by their special mechanism a high degree of hybridity balanced by a low degree of crossing-over. They have sacrificed future variability to present variation, for as the system becomes more highly specialised, gametically and zygotically, crossing-over and mutation are more severely restricted and the species finds itself in an evolutionary blind alley. The changes that it has undergone with advantage in the first stage prove irreversible and presumably fatal in the last. This is the position of *Rhoeo discolor* with a ring of twelve chromosomes. The single surviving representative of its genus, it is restricted in distribution and almost invariable in form.

The device of complex hybridity undoubtedly leads to ultimate extinction. But it reveals to us a mechanism of chromosome differentiation by the suppression of crossing-over which in this essential is similar to that used by the higher animals in controlling their mating system and in fostering hybridity. The special difference is that the mechanism of genetic sex differentiation in animals is self-renewing as well as self-destroying.

CHAPTER XVII

THE EVOLUTION OF SEX

THE origins of sexual differentiation between gametes, distinguishing large stationary eggs from small motile sperm cells, can be seen in the Protozoa and Algae where all degrees of differentiation occur. In its simplest and probably original form this differentiation was a differentiation within the individual which therefore bore cells of both kinds. Most of the higher plants are still hermaphrodite, bearing both pollen and eggs. They have, as we saw, various special devices which assure cross-fertilisation. This end is achieved in most of the higher animals by having the sexes separated in different individuals. Here and there in a number of different families of plants we can see the same mechanism of sex differentiation coming into existence. In animals it is long established and indispensable. In plants it is a sporadic and short-lived alternative to other systems.

An experiment with *Zea Mays* provides the clearest evidence of how the mechanism can develop. One recessive mutation (*ff*) in the pure state causes sterility of the female flowers, which are on separate inflorescences from the male. Another mutation in the pure state (*mm*) converts the male flowers into female and the fertility of these is unaffected by the action of the *ff* gene. Plants of the constitution *ffmm* are entirely ovule bearers. Plants of the constitution *ffMm* are entirely male. A stock therefore which contains these two types in equal numbers will produce offspring with them likewise in equal numbers. The male is the hybrid sex. Provided such a new stock is isolated, genetically or geographically, from the original stock its system will be stable and self-perpetuating. An inversion including *f* and *m*, if they are near together will give the necessary isolation. It remains to be said that it has proved equally easy, using different mutations, to produce a stock in which the female instead of the male is the hybrid sex.

There is no doubt that in many plant species sexual differentiation is little more advanced than in this experiment. Nevertheless such a system is not likely to persist unchanged. So soon as the two types, male and female, are permanently segregated in the species, each will have special needs calling for special genetic adaptations. This can take place in one way alone, by the occurrence of mutations absolutely linked with the segregating *M–m* genes. Mutants linked with *m* will be selected if they are recessive and favour the female. Mutants linked with *M* will be selected if they are dominant and favour the male.

We usually call the *m* chromosome *X* and the *M* chromosome *Y*. Between them there is this essential distinction: the *X* chromosome occurs in both sexes, the *Y* is restricted to one sex and never meets or crosses over with an identical partner.

The *XY* sex is usually male, the *XX* female. The opposite holds good in birds and Lepidoptera. In dioecious mosses and liverworts the diploid generation is always *XY* and the haploid generations *X* and *Y*. There is then no evolutionary difference between *X* and *Y* and the female individuals are arbitrarily allotted the *X*.

Thus an important discontinuity between the *X* and *Y* chromosomes and between the sexes which they determine arises, subject to a suppression of crossing-over between them or rather between parts of them. What methods of suppression of crossing-over are available we have already seen. Genotypically a localisation of chiasmata or structurally an inversion of the segment of chromosome containing either the *M* or *m* genes will suppress crossing-over near these genes and make a system of sexual specialisation possible.

The available evidence shows that genotypic control is primarily responsible, structural change secondarily. Thus the *XY* sex always has lower crossing-over than the *XX* sex, in the other chromosomes as well as in the sex chromosomes. The extreme example of genotypic control is found in *Drosophila*, where as we saw crossing-over is abolished in the *XY* sex, that is in the male. Such a general reduction can only be genotypic. Structural changes are likely to follow this genotypic suppression and are responsible, as we shall see, for great variation in the *Y* chromosome. The consequences of this suppression are seen when we compare the differences between *X* and *Y* chromosomes in various plants and animals. The different degrees of divergence between them fall into an evolutionary series.

The earliest stage of differentiation is that found by Winge in *Lebistes reticulatus* in which the males are *XY*. Free crossing-over of many genes is possible between *X* and *Y*. Only one, apart from the sex differential itself, is completely restricted to the *Y* chromosome; possibly the two genes lie in a small inverted segment together. Now certain stocks have a gene in one of the autosomes, i.e. in one of the chromosomes other than *X* or *Y*, which when pure turns the *XX* fish into a male; in the hybrid state for this gene the fish is a female. Thus we have the beginnings of a system in which the old male type with its *Y* chromosome is eliminated and the female becomes the hybrid or *XY* sex, while the new male becomes the pure or *XX* sex. The related genus *Aplocheilus* has such a system. In the course of the evolution of the mammals some such change as this must have occurred once, if not several times, because the female is the hybrid sex in reptiles as well as birds, and the male in mammals (Fig. 21).

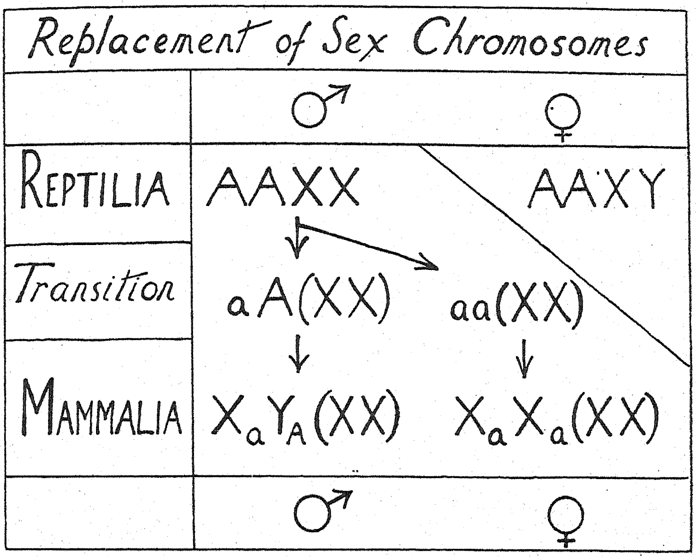

Fig. 21. The evolutionary stages by which a pair of autosomes (*AA*) can become the sex differentials in the *XX* sex, thus making it possible for the old *XX* sex to become the *XY* sex. The *Y* chromosome can also be displaced by direct loss as in Fig. 22, giving an *XO* system which itself can also be replaced as above by a new *XY*.

Now, so far as the *Y* chromosome is concerned, the species bearing it is a permanent hybrid. In the part carrying the sex differentials, crossing-over is suppressed and its position must always be that of a chromosome in a permanent hybrid species of *Oenothera*. It must be made up of two segments, a *pairing segment* in which a chiasma is formed, and crossing-over occurs, with the *X* chromosome, and a *differential segment* containing the sex-bound genes.

The behaviour of *X* and *Y* chromosomes between which differences are developing depends on the position of the differential segment in relation to the centromere. In the commonest types it lies next to the centromere, or includes it, as it does in *Oenothera* and other permanent interchange hybrids. Such a proximal differential segment occurs in the plants *Humulus* and *Rumex*, in both of which genera species occur with the *Y* fragmented in its differential region. The two ends of the *X* then each pair with a small *Y*; the female is *XX*, the male XY_1Y_2.

In the mammals the pairing segment is proximal, usually on both sides of the centromere, and the differential segment distal. This has various interesting results. In the rat there is a single long differential segment in one arm of the *X* and little or none in the *Y* (Fig. 22). A chiasma may be formed in the short arm of the pairing segment opposite the differential segment. This chiasma moves to the end and the two chromosomes separate reductionally, as is said, at the first division. When however a chiasma is formed in the longer arm between the centromere and the differential segment, the two chromatids of this segment become attached to two different centromeres and the bivalent divides equationally at the first division, reductionally at the second (Fig. 5).

Owing to these chiasmata being formed at various points in the pairing segment we should expect that particular gene differences would cross over from the *X* to the *Y* chromosome and vice versa. Such gene differences would be more or less closely linked with the differentiation of sex instead of being absolutely linked, or rather bound, to *X* or *Y* like those in the differential segment. Without careful tests they would not be distinguishable from autosome differences. A number have now been recognised in man.[1]

Species of *Drosophila*, which also have proximal segments, are distinguished from the mammals by two remarkable properties of these segments. They always unite in the male by two reciprocal

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[1] Haldane, 1936.

chiasmata between *X* and *Y*. Lying as they do very close to the centromere, they are entirely inert except where they abut on the differential segment. Where a single gene difference is known, affecting the length of the thoracic bristles, this gene, "bobbed", sometimes lies between the two reciprocal chiasmata and so crosses over from the *X* to the *Y* chromosome like the loosely linked characters found in man. Since the two reciprocal chiasmata in *Drosophila* exactly compensate for one another in crossing-over it is possible for a differential segment to be maintained on either side of the pairing segment, and this condition is in fact found in several species.

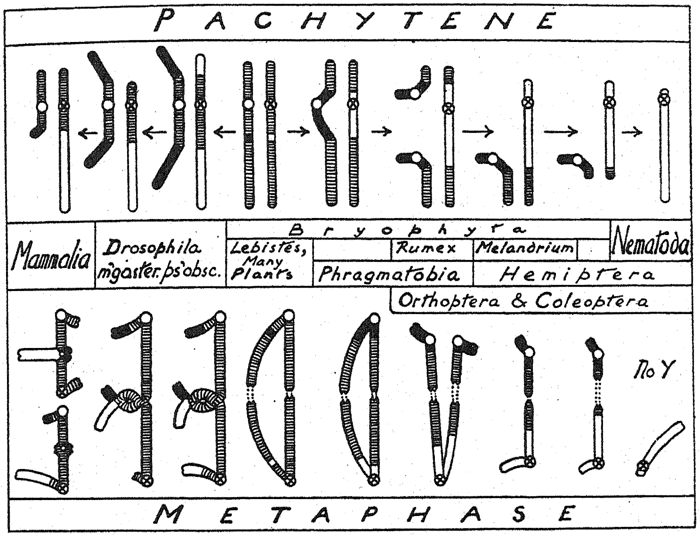
PACHYTENE
Mammalia
Drosophila
m'gaster. ps'obsc.
Bryophyta
Lebistes,
Many Plants
Rumex
Melandrium
Nematoda
Phragmatobia
Hemiptera
Orthoptera & Coleoptera
No Y
METAPHASE

Fig. 22. The evolutionary divergence of *X* and *Y* chromosomes, shown by the pachytene pairing and metaphase association, following two series according to the relative positions of centromeres and differential segments (white in *X*, black in *Y*). Pairing segments hatched. The mammalian type corresponds to the unequal chromosomes illustrated in Fig. 5.

The evolution of the sex chromosomes depends on the genetic history of the differential segments. The differential segment of the *X* is not in a very remarkable position, since it can cross over with its homologue in an *XX* individual. That of the *Y* on the other hand is in a very special position; it occurs only in the hybrid condition, and is totally precluded from crossing over there. The evidence from mammals and insects is that in these groups it has become almost entirely inert. In the differential segment of the *X* chromosome of man a very large number of gene differences have been detected; in that of the *Y* only four. In *Drosophila melanogaster* the same is true, but in spite of this lack of mutations the genes are not entirely inert. A male with an *X* and no *Y* chromosome (*XO*) entirely resembles a normal male in form but it is sterile. Meiosis is abnormal and the sperm degenerate.

The capacity for free combination within the autosomes evidently gives them such an advantage in adaptive efficiency over the *Y* chromosome that they come to take over its work. The decisive difference between the sexes comes to be the difference in proportion of the *X* and the autosomes.[1]

Two sets of autosomes and two *X*'s give a female; two sets of autosomes and one *X* give a male, irrespective of the number of *Y*'s which may be added to each. Further, three sets of autosomes and two *X*'s give an intersex. What we have seen earlier shows us that this change of balance is not essentially different from gene mutation. The effect of the change is merely more crudely obvious because it is on a larger scale.

The consequences of the *Y*'s inertness are felt in two ways. First, the *Y* begins to vary very freely in size, not only as between related species of mosses or insects but also within the same species, e.g. in the neuropteran *Chrysopa vulgaris* and in *Drosophila pseudo-obscura*, as well as in species of *Humulus* and *Rumex*. Secondly, in certain large groups of insects (as we saw) and nematodes the *Y* chromosome has entirely disappeared. In any organism any chromosome is liable to be lost, particularly through failure of pairing at meiosis. If it is lost and the loss makes no difference the species will continue without it.

In the Coleoptera and Hemiptera we can see all the stages in diminution of the *Y* chromosome, ending in many species in its total loss. In the last stages the pairing segment is so reduced that pachytene pairing of *X* and *Y* no longer takes place, crossing-over is completely suppressed and the chromosomes segregate following

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[1] Bridges, 1922.

momentary contact of their terminal pairing segments at metaphase. When supernumeraries arise from fragmentation of the *Y* they can mount up to the number of six without effect. They are evidently inert. In the Orthoptera this process has gone even further. In the whole order, apart from some Mantidae, the *Y* has disappeared.

When the *Y* is lost the males have a single unpaired *X* chromosome at meiosis (Figs. 3 and 22). This univalent is somewhat more regular than other univalents and in most species divides either always at the first or always at the second division. Occasionally however, as in the bug, *Vanduzea*, it is less settled in its behaviour and divides at either division, just as a univalent will do in many plant hybrids. Like other univalents it lags behind the bivalents if it divides at the first division. Sperm are produced in equal numbers with and without *X*. This is the last stage in the evolutionary breakdown of the *XY* system.

A genetic method of sex differentiation occurs in many animal groups which in its origin seems to be unrelated to the alternative *X–Y* system. The females are diploid, the males haploid, arising from unfertilised eggs. This system is found in Rotifera, Acarina and four orders of insects, Thysanoptera, Hymenoptera, two families of Hemiptera and one of Coleoptera, represented by a single species *Micromalthus debilis*.[1]

This system has evidently arisen independently in these groups and its origin is indicated by the behaviour of a coccid bug, *Icerya*, where a diploid hermaphrodite and a haploid male coexist in the same species. The different tempo of development in a haploid might readily give a different emphasis to one sex, as it does in crosses between species. The advantage of having the sexes separate would then lead to the suppression of the maleness in the diploid.

The effectiveness of this explanation is shown by there being haploid males in six groups and haploid females in none. Haploid males are due to lack of fertilisation by males and make good the defect to which they owe their origin. They therefore have an immediate advantage if they are acting in equilibrium with another system of reproduction (the hermaphrodite) but none if they are derived gradually from the *XY* sex.

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[1] Schrader, 1928; Scott, 1936.

A great number of different mechanisms may be used to separate the sexes on different individuals. In the types we have taken, segregation of dissimilar chromosomes at meiosis or differential fertilisation is the basis. In certain species, both of plants and animals, the external conditions of development may determine the future sex. In the sea worm *Bonellia* and elsewhere eggs falling free develop into females, eggs falling on to females develop into males. The genotype of the species is such that it makes this differential response which is adapted to its reproductive requirements. The end result is the same whether it has been achieved by the action of external or internal differences. It may equally remain the same above all the increasing elaboration that we see in the internal mechanism of segregation. Beyond a very early stage we need not suppose that any necessary increase in elaboration takes place in the physiological differentiation of sex. The mechanism has to change merely to keep pace with the mutations and structural changes which are constantly disintegrating it. It is less stable than the external differentiation it determines. The mechanism of segregation, however elaborate, merely releases a trigger which directs the processes of development along one of the two alternative paths of sex.[1] There is some evidence that even in the most advanced stages of developing this trigger, in *Drosophila*, it may be suddenly replaced by an entirely new device, much as in *Lebistes*. And the new system will work as well as the old.

The evolution of sex chromosomes shows a principle in common with that of permanent hybrids. The suppression of crossing-over between two homologous parts of chromosomes separates them in evolution as effectively as if they belonged to different species. The discontinuities that arise as a result are of the same order as those arising between species. The discontinuities that we see arising and developing within species when protected from crossing-over by inversion hybridity as well as by other kinds of isolation have the same adaptive significance. The two sexes are in fact two species mutually adapted for reproductive processes.

The evolution of the sex chromosomes shows a second principle which may be expressed in very general terms. Two chromosomes are taken out of the set and subjected to different conditions of recombination and therefore selection from the rest. But their properties of genic and structural change are necessarily the same as the rest. This evolutionary disharmony may be stated in a simple way; the directive agent of change in the autosomes is selection, in the sex chromosomes mutation.

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[1] Muller, 1932*a*.

The result is that no permanent balance can be set up between them. The sex chromosomes pass through a perpetual cycle of disintegration and replacement, no stage in which is physiologically preferable to any other.

CHAPTER XVIII

STERILITY: THE CONTRADICTION

A MATURE zygote must inherently have arisen from the fusion of viable gametes which have given a viable product. The problem of sterility is how such a zygote can itself produce gametes, or its gametes produce zygotes, that are not viable; in other words how it can form gametes unlike those from which it is derived. It may do so under three kinds of conditions. First, an unfavourable environment may prevent development taking the same course as it has taken in the past. Secondly, differentiation may fail to provide uniform conditions of reproduction. A production of an excessive number of egg cells, or of unfavourably placed egg cells, where the young offspring are nursed by the female parent, may result in the destruction of some. All other instances of failure of development of gametes and zygotes fall into the third class. They are due to genetic variation.

Variational sterility is in the simplest case *relational*. It arises from crossing dissimilar forms. The parents may fail to copulate in species crosses of animals. The pollen may fail to germinate on the style or grow down it in cross-fertilisation between races or species. The same is true *mutatis mutandis* in animals. These obstacles to fertilisation are physiologically similar to those producing self-sterility in hermaphrodite plants and animals, where as we saw they are due to lack of genetic differences. A specific gene mutation is known in *Zea Mays* to cause cross-sterility.[1] Or again the new zygote produced may fail to develop beyond an early stage, either in the simplest case owing to its new and untried genetic constitution being unsatisfactory or, in the mammals, owing to the relationship of embryo to mother being unsatisfactory. In the higher plants the endosperm also plays a part. This can be most simply shown in the occurrence of reciprocal differences between diploid and polyploid plants. Each of these types of sterility involves physiological problems peculiar to the particular case. The effect of all of them is to restrict the size of the endogamous group by genetic isolation, and they act as a direct limitation, as we shall see, on all the other types of sterility.

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[1] Demerec, 1929.

The second and third kinds of variational sterility may be described in more general genetic terms. They occur irrespective of cross- or self-fertilisation. The second is *genotypic sterility* and is due to the organism being different from its parent or parents in having some abnormality of its reproductive processes determined by its individual genotype. Such sterility may take effect (equally in maize or *Drosophila*) at any stage of development. It arises earliest by the abortion of the sexual organs, later by the suppression of chromosome pairing at meiosis through lack of precocity and last of all by a failure in the development of the germ cells which have been satisfactorily formed. These genotypic properties may appear as a result of a mutation or in a cross between two races or species. Usually in either case they affect one sex alone. And usually in plants the anthers are more susceptible to abortion than the ovules, but in *Zea Mays* and *Rubus Idaeus* mutations are known affecting each separately. Such mutations may be used as we saw in establishing sexual differentiation. In animal crosses where the sexes are separated on different individuals it is usually the hybrid sex which is sterilised in this way.[1] The reason for this is fairly clear. The XX sex has one X and one set of autosomes from each parent, the XY or XO has no X from one parent and the Y being largely inert does not take its place. The hybrid sex is as we may say unbalanced. The result is that in crosses between races of *Drosophila pseudo-obscura* the pairing of the chromosomes is suppressed at meiosis and the testes are under-developed. In the female however the chromosomes pair and the eggs are fertile if back-crossed to one of the parents. Some of the males in this back-crossed generation are fertile. They no longer have the wrong combination of X and autosome genes.[2]

The third kind of variational sterility, and the one which we are in a position to analyse most exhaustively, is due to a lack of uniformity in the products of segregation, i.e. to the formation by a zygote of gametes genetically different from those which gave rise to it. We may describe it as *segregational sterility* and we may consider it in relation to the three kinds of hybrids in which it occurs, gene hybrids, structural hybrids and numerical hybrids, using at the same time the special behaviour of tetraploids of hybrid and non-hybrid origin as a test of our conclusions.

[1] Haldane, 1931.

[2] Dobzhansky, 1937.

We may see the effect of segregation on sterility most simply in a triploid plant. Spores are formed with all numbers of chromosomes between the haploid and the diploid. Those with intermediate numbers are unbalanced. They develop on the female side to produce egg cells. On the male side however on account of the longer life of the spore a proportion usually die before the pollen grain germinates. When they survive the balanced and unbalanced grains have to compete in growing down the style; only a small proportion succeed in fertilising the egg cells, and these are likely to be the balanced ones. When a triploid is crossed as a female with a diploid as a male the result is therefore a higher proportion of unbalanced progeny than in the reciprocal cross. This is notwithstanding a certain differential mortality among the young embryos which also reduces the proportion of unbalanced ones. When the triploid is the male parent very few progeny except diploids and simple trisomics are usually produced.

Sterility of a triploid is thus due to unbalance in the progeny. Now there are occasional plant species which do not show any serious effect of unbalance. This is sometimes due to the basic set being itself polyploid in origin, and sometimes to there being so much translocation and duplication of segments of chromosomes that a mechanical diploid is physiologically a high polyploid. This is evidently true of *Hyacinthus orientalis*, $n=8$, for in this species different plants with 23, 24, 27 and 30 chromosomes are almost equally vigorous. In this species also the triploids are as fertile as diploids.

Absolute deficiency is an even more serious cause of sterility than unbalance. *Rhoeo discolor* having a ring of twelve chromosomes can produce, through errors in the orientation of the ring, pollen grains with five and seven chromosomes instead of six. Those with five never reach the first mitosis. Those with seven may even grow down the style. They never give rise to offspring, for the seedlings all have the same uniform number and appearance as the parent.

These examples show us why a hybrid like *Raphanus-Brassica* is sterile. Owing to lack of pairing, pollen grains and embryo-sacs are produced with all numbers and combinations of chromosomes; none of the parental types are reproduced except by a rare chance, and a balanced combination will arise only by complete non-reduction.

In an entirely opposite way as we saw following complete pairing and crossing-over in every chromosome of the diploid *Primula kewensis* the original parental combinations are even less likely to be produced and in consequence likewise the hybrid is absolutely sterile. In the tetraploid through pairing and segregation of similar chromosomes, uniform and balanced gametes are produced and the plant is fertile.

The position of an autotetraploid is significantly different. Its chromosomes change partners at pachytene in all plants and, when they are long, in animals, and, forming chiasmata in these different associations, they remain quadrivalents at metaphase. These quadrivalents are, except perhaps under very special conditions, incapable of regular orientation and segregation in every cell. With linear orientation three and one segregation often results. In this way a tetraploid cherry with eight potential quadrivalents has given a segregation of 19 : 13 instead of 16 : 16. With indifferent diamond-shaped co-orientation of the four chromosomes two may be left on the plate at anaphase to divide as univalents. Moreover, trivalents and true univalents often occur (Fig. 23).

The autotetraploid thus yields unbalanced gametes and its fertility is reduced. The sterile diploid gives a fertile allotetraploid. The fertile diploid gives an infertile autotetraploid. There is a negative correlation between the fertility of diploids and that of the tetraploids they give rise to. Hence autotetraploids in nature do not usually establish themselves as new species unless sexual fertility can be to some extent dispensed with. By discovering their occurrence among plants we are therefore indirectly discovering the degree of importance of sexual fertility in the life of the species, a matter to which little attention has been paid in the past.

Let us return with the information which these special examples give us to consider sterility within a natural diploid endogamous group of common size and stability, a group within which cross-fertilisation takes place between pairs of gametes all of which differ in respect of a varying number of changes in genes and in their arrangement. We find that a proportion of the zygotes produced fail to develop and we can trace this failure to the recombinations that occur at meiosis. Sometimes it is due to crossing-over within inversions giving deficient gametes and zygotes. Sometimes it is due to irregularity in segregation following failure of pairing at meiosis. Sometimes it is due to two chromosomes which are necessary to one another failing to pass to the same gamete. They may be complementary to one another either through one containing a segment of chromosome actually removed from the other (as we see was the case in *Oenothera*) or they may contain independent mutations which cannot work separately. When an endogamous group develops cross-sterility within it, as we saw earlier, or when genetic diversity within it reaches such a pitch that crosses between divergent individuals (such as diploids and tetraploids) are absolutely sterile, the group breaks up into two. Sterility brings its remedy. The new smaller groups having less variation within their limits are less sterile than the old. But if cross-sterility does not readily develop, or if sexual reproduction can be to a great extent dispensed with, as in some sections of *Rosa* and *Rubus*, a population will arise which will vary between moderate fertility and absolute sterility and a population moreover in which the discontinuity of species is no longer recognisable.

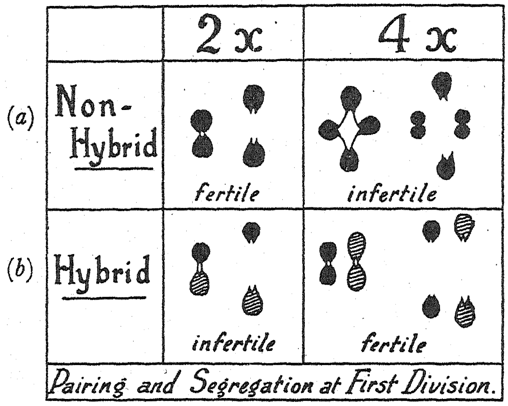

Fig. 23. Diagram showing the alternative conditions of segregational sterility (*a*) in a hybrid diploid, (*b*) in a non-hybrid tetraploid. (After Darlington, 1932*a*.)

Sterility is therefore the contradiction inherent in variation and recombination. A stock that is invariable will become pure breeding and completely fertile. Even if it varies, and yet suppresses the recombination of variants that would occur by the crossing of individuals or by the crossing-over and segregation of chromosomes, it will still remain pure-breeding and completely fertile. Sterility is the price the species pays in the death of its immediate progeny for the advantages of recombination and adaptation in its more remote posterity. It may be said that this price is inevitable. That is not true for every group of plants and animals; there are some species which avoid paying it. We will now see how they do it.

CHAPTER XIX

APOMIXIS: THE ESCAPE

In most organisms reproducing sexually the egg does not develop until the sperm nucleus or generative nucleus of the pollen fuses with its nucleus or is about to do so. Without a sequence of this kind sexual reproduction could not have been established. But the sequence is not, for all organisms and under all conditions, as obligatory as might be supposed. With eggs of frogs, sea urchins and seaweeds it may be replaced by artificial devices such as shaking or pricking, or by alteration of the surface conditions with specific reagents. In plants, pollination often suffices, and if the pollen is of a different species in *Datura* or in *Rubus* it may fail to enter the egg, which then develops without fertilisation. The stimulus of development has then become indirect, like that of a conditioned reflex. In cotton (*Gossypium*) and in the threadworm *Rhabditis* special stocks regularly allow the development of their unfertilised eggs.

One might suppose that, where this parthenogenesis was occasional and accidental, it merely occurred after the normal time of fertilisation had passed. Very often supernumerary egg cells in a plant will be stimulated to develop in this way merely by the fertilisation of their sisters. The development of a haploid egg cell to maturity depends however on its genetic constitution. In a group with a high hybridity equilibrium many recessive mutations such as would have a depressive effect in the pure condition are floating in the population protected by a hybrid condition. A haploid being pure and unprotected must always reveal these recessives. Haploid parthenogenesis giving mature progeny is nevertheless known in thirty genera of flowering plants. But it is commonest in the relatively inbred stocks found in some cultivated plants and in polyploid species where the "haploid" is itself physiologically diploid or polyploid. Non-reduction is therefore often necessary with parthenogenesis, not merely to maintain the two together as a permanent system, but also to permit the survival of the egg which goes unfertilised. And the casual occurrence of parthenogenesis combined with non-reduction will generally pass unnoticed. It seems therefore that the observations of haploid parthenogenesis, abundant though they are, must give an inadequate notion of the widespread occurrence of this capacity of egg cells to develop without fertilisation.

The various combinations of non-reduction and non-fertilisation under cover of the external forms of sexual reproduction are known as apomixis. How do they arise in nature? It is possible that apomixis is sometimes thrust upon a sexually fertile stock by mutation or exceptional conditions causing both the compensating aberrations to occur at once. This has happened in *Rhabditis* in experiment. A strain arose by mutation in which reduction was suppressed and the egg developed without fertilisation. Such a strain would have a longer or shorter lease of life in nature according to the merits of the sexual type from which it came.

Obligatory parthenogenesis is more likely to get into a fertile species indirectly. In Aphides summer broods are parthenogenetic. This merely economises the sexual processes by dispensing with the males. It lengthens the sexual cycle just as paedogenesis broadens it. Males are produced by the parthenogenetic females under colder conditions and a sexual generation arises; the XX female gives an XO male by loss of one X chromosome at the single non-reductional division which replaces meiosis. When such a species spreads to a warmer climate the sexual generation is omitted. Obligatory parthenogenesis has got in by the back door.[1]

The general condition for the suppression of sexual reproduction in plants and animals is however sterility. Sterility may act in two ways. A new tetraploid animal of a sexually differentiated kind can scarcely survive as a male, since it must cross with diploid females and yield normally sterile triploid progeny. A new tetraploid female can survive however if her eggs will develop without fertilisation. She can perpetuate herself as a tetraploid if in an early cleavage division doubling of the chromosomes occurs to compensate for lack of fertilisation. Such is the behaviour of the moth *Solenobia triquetrella* and the crustacean *Artemia salina*; both are polyploid and parthenogenetic.

The position of the triploids is even simpler. Their inherent segregational sterility cuts them off from sexual reproduction at once. Triploid species can survive only by apomixis or by vegetative propagation. Moreover owing to the awkward segregation of trivalents and univalents they are particularly likely to have a completely abortive first division in meiosis and thus to produce two triploid products of meiosis instead of four irregularly reduced ones. At one stroke triploidy can remove the possibility of reduction and the need for fertilisation. If in a triploid the egg cell can develop without the stimulus of fertilisation, apomixis is thus automatically established. Such is its origin both in the isopod *Trichoniscus elizabethae* and in many species of flowering plants, for example in *Hieracium*, *Taraxacum* and *Artemisia*.

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[1] Vandel, 1927.

These examples make it clearer what is the origin of apomixis in diploids. In the triploid we see that hybrid sterility must be the immediate cause since an act of hybridisation, the fusion of diploid and haploid gametes, was the last sexual act in its history. In the diploid any condition that would give the result of sexual sterility and permit a failure of reduction would have the same result. Since we see these conditions arising both by hybridisation and by special genotypic combinations in all groups of plants and animals, while apomixis is specially frequent in certain groups, the limiting condition must be the capacity of the egg to develop without fertilisation. This capacity gives the sterile hybrid or the sterile mutant a means of escape from its sterility.

Just how this capacity works is shown by those species of plants which we may describe as genetically *versatile*. Some such species, like the diploid *Allium odorum*, resemble the aphides. The normal egg is capable of development only after fertilisation. Sometimes however a bud in adjoining tissue grows into an embryo-sac with an egg nucleus and its seven customary attendants. But this embryo-sac is purely vegetative; its nuclei are diploid and its egg cell divides without fertilisation. Why should this development sometimes replace the normal embryo and sometimes not? The answer is provided by experiments with similar species of *Rubus* and *Poa*. When fertilisation is attempted with pollen of a closely related plant it is successful, with that of a different species it is usually unsuccessful; the union is a false one for, although seeds are obtained, they are apomictic. Evidently the vegetative embryo develops when the sexual one fails.

The evidence of competition between sexual and vegetative embryos reminds us of the competition between potential embryo sacs of different genetic constitution in *Oenothera*. This competition amongst embryo-sacs is probably very common in hybrids generally although nowhere else studied in genetically controlled material. It shows a struggle for existence between cells and between individual embryos within the ovule analogous to that between free growing plants. Its effect is like facultative parthenogenesis in the aphides, an economy in the reproductive resources of the species.

	FERTILISATION	NON-FERTILISATION
REDUCTION	Sexual Reproduction	Haploid Parthenogenesis
NON-REDUCTION	Polyploidy	Diploid Parthenogenesis Vegetative Embryony
REPRODUCTIVE METHODS OF VERSATILE SPECIES		

Fig. 24. The combinations of reproductive methods found in versatile species, sometimes all in the same plant competing with one another.

Genetic versatility probably reaches its extreme in certain polyploid species. In *Poa pratensis*, for example, we may have every conceivable combination of reduction and non-reduction on one or both sides with fertilisation and non-fertilisation. Thus a $12x$ plant when crossed with an $8x$ plant may yield $6x$, $10x$, $12x$, $14x$ or $16x$ progeny. The particular types of progeny will depend again on their success in competition as well as on the sexual propensities of the parent. For example since the numbers actually found in the species do not generally range beyond the extremes of $6x$ and $18x$ it is clear that non-reduction must be more successful with $6x$ plants and non-fertilisation with $18x$. The non-reduction is occasioned apparently by high autopolyploidy, which at the same time makes it possible for the progeny to forgo fertilisation without exposing too many undesirable recessive combinations and also makes it possible for plants with unbalanced chromosome numbers to show very little effect of unbalance[1] (Fig. 24).

What happens to a stock after it has completely surrendered its sexual mode of reproduction? If meiosis is completely suppressed and no crossing-over occurs between the chromosomes it is clear that apomixis becomes merely a vegetative process under a cloak of sexual reproduction. All recombinations ceasing and mutation still having a rate adapted to the needs of a species with recombination, the apomictic species will lose its genetic resiliency and after a brief prosperity succumb to a changing environment, preserving to the last the unwanted devices of its sexual apparatus.

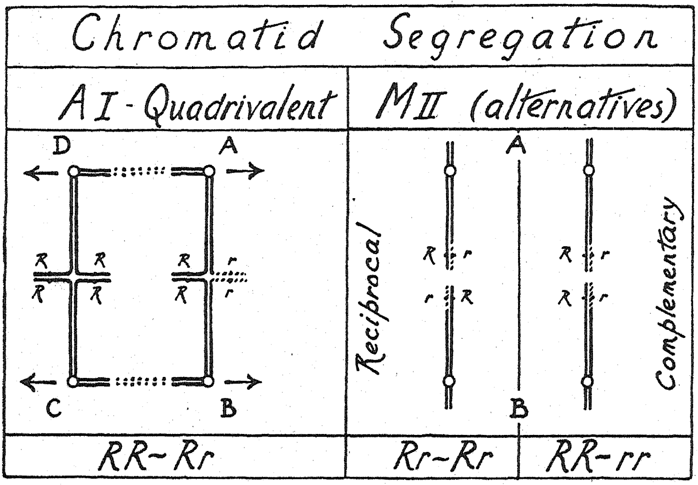

Fig. 25. The results of two chromosomes (*A* and *B*) passing to the same pole after having undergone crossing-over. This happens normally with quadrivalents in autotetraploids and with suppression of the first division in a parthenogenetic diploid. In half the cases the segregation at the second division is complementary so that the products are dissimilar (although with parthenogenesis the chromosome number is not reduced). A particular gene difference *R–r* is used as an indicator. In the tetraploid an *RRRr* individual can thus give *rr* gametes. In the parthenogenetic diploid an *Rr* parent can give *rr* progeny.

In many apomictic plants however crossing-over is not abolished along with reduction. The first meiotic division may be suppressed and a single unreduced nucleus be reformed although many chromosomes have paired, even as we saw in a triploid on account of multiple pairing. These chromosomes have crossed over with one another. The two chromatids attached to the same centromere are no longer always sister chromatids but come in part from different chromosomes. Perhaps if the plant is a triploid or structural hybrid they come from widely different chromosomes. These chromatids will pass to the same pole as their true sisters in half the second divisions in which they occur. Wherever there is crossing-over there will therefore be a limited amount of segregation (Fig. 25) even though there is non-reduction. The amount of segregation and recombination will be *subsexual*.[1]

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[1] Åkerberg, 1936 and unpublished.

In this way the new apomictic species will have a limited scope of recombination and variation so long as pairing and crossing-over can take place between its chromosomes. The result is shown by the appearance of mutants in experiment, and innumerable trivial species in nature, in such genera as *Hieracium* and *Taraxacum*. It is also probably shown by the development of a more precise and fertile system of apomixis. The abandonment of sexual reproduction is progressive and irrevocable. Meiosis is completely suppressed on the female side; it is replaced by a single non-precocious mitosis. The last agent of recombination is destroyed. All these stages of development can be seen within the genus *Hieracium*.[2]

Thus we see apomixis saves what can be saved when sexual fertility has been lost. Sexual reproduction provides in recombination the basis for the adaptation of all its posterity. Apomixis provides for its immediate progeny. It retains in some species a few relics of the sexual system which give it the means of postponing extinction and even developing a momentary efflorescence of new forms. But with the loss of sexual recombination the apomict, like the permanent hybrid, is cut off from ultimate survival. Apomixis is an escape from sterility, but it is an escape into a blind alley of evolution.

[1] Darlington, 1937*a*.

[2] Gustafsson, 1934; Darlington, 1937*a*.

CHAPTER XX

THE INTEGRATION OF THE CELL

THE first problem of heredity is that of the parts played in it by the nucleus and the cytoplasm. It is also the last, for we can deal definitely with the indefinable cytoplasm only when the nucleus has been accurately defined. When we consider the cytoplasm we have to leave behind for the most part the visible determinants which are so useful in dealing with the nucleus and rely solely on inferences from heredity and development. These inferences are less obvious but none the less rigorous. Our next task must be to separate heredity from development, and in order to do this we must know something about how genes act during development. We have already considered much of the evidence in special connections. Let us now bring it together.

Cells can exist without nuclei. Special cells like red blood corpuscles are even adapted to do their specialised work for a limited period without nuclei. But they do not grow or multiply. Egg cells deprived of their nuclei quickly die. Successful regeneration of parts of unicellular organisms depends on the presence of the nucleus. In short the nucleus is constantly acting on the cytoplasm.

Now we know that the action of the nucleus is balanced. Its different parts produce a co-ordinated effect. Does this co-ordination take place inside the nucleus? The exception in this case proves the rule. The position effect of genes which we saw earlier shows that exceptionally two genes have a different effect if they are close together in the chromosome from what they have if they are far apart. Here then their products must interact inside the nucleus. As a rule they probably do not. They interact in the cytoplasm and through it.

The intermediacy of the cytoplasm is perhaps most obvious in the genotypic control of chromosome behaviour, since the uniformity of the action of the nucleus on itself presupposes a reaction with its substrate. Hence the old fallacy that it was indeed the cytoplasm which ultimately controlled nuclear behaviour and not the nucleus itself.

The next question is how quickly the nucleus can act on the cytoplasm. This is shown best by the examples of extreme individuality in the nucleus. In the fertilisation of *Habrobracon* the sperm nucleus is believed to choose, as it were, instantaneously which of the two products of the second meiotic division in the egg it will fuse with. In the diploidisation of fungi the guest nucleus divides in every cell it enters, the host nucleus does not. In both instances a single gene difference may be all that distinguishes the two nuclei. More important differences distinguish pollen grains and potential embryo-sacs which live or die according to whether they have the right or the wrong numbers of chromosomes or genetic complexes. And here we may note that precisely the same difference of viability that marks certain genetic complexes in *Oenothera* may be determined, and usually is determined elsewhere, by relative position of the nuclei in the organism. We shall return to this later.

Some genes therefore act as quickly as diffusion in a liquid substrate can allow them to act. And multiple differences are therefore likely to act rapidly. But individual genes differ in their time of action.[1] They are set going at a specific time in development. Thus the detailed properties of pollen grains—shape, colour and kind of starch—are usually determined by the genetic action of the mother plant, although if this plant is hybrid for genes affecting these properties the pollen grains will differ in these genes. Exceptionally however in *Zea*, *Oryza*, *Sorghum*, *Pisum* and *Oenothera* the pollen grains show their own specific properties. In a word the genotype reacts with the cytoplasm and the cytoplasm changes its properties throughout development. These properties at any one stage are the resultant of the *reactions* of the genes at all previous stages—including the preceding generation.

These changes in the cytoplasm are most highly developed in animals. They are derived from an original asymmetry in the egg and persist throughout development and not merely in space but also in time. The different parts of the animal at one time are as different from one another as are the same parts at different times. Their interrelations in time and space are established by the formation and diffusion of chemically recognisable organisers.[2] Thus we have evidence that the integration of gene action is due to the reactions between genes and cytoplasm being chemically and spatially determined in a specific succession and arrangement.

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[1] Haldane, 1932.

[2] Waddington, 1939.

The delayed effect of the cytoplasm is shown by the preponderant influence of the egg on early development where its recent genetic history is widely different from that of the sperm nucleus. This is shown most crudely by the breakdown of development in most distant hybrids in animals, whether in sea-urchins, fishes or amphibia. This breakdown is always associated with gross malformations. The same breakdown follows in animal eggs where the egg nucleus is removed and a sperm nucleus from another species allowed to develop in the maternal cytoplasm. Here it can sometimes be shown that the early development is maternal and the breakdown occurs when the nucleus tries to assert itself.[1]

Less violent conflicts between nucleus and cytoplasm arise through the treatment of *Paramoecium* or *Drosophila* with heat or various poisons. Abnormalities are produced which are inherited only through the egg (in *Drosophila*) and persist for a limited number of generations.[2] Specific differences showing the same maternal influence are found in several crosses between animal species and races and indicate a prolonged failure of the cytoplasm to adjust itself to the nucleus. Whether any such cases imply the absolute independence and permanence of the cytoplasmic elements concerned is doubtful. For the moment we can consider these examples as showing at least a high degree of integration in the cytoplasmic system.

So much is true of animals. In the past the same rules have often been thought to apply to animals and plants in regard to cytoplasmic effects, because the same rules apply in regard to nuclear effects. This is certainly not true. Not only are the processes of development less highly organised in plants and regeneration, especially in the lower plants, vastly easier, but the genetic results tell quite a different story.

"Hybrids", containing the nucleus of one species and the cytoplasm of another, live and flourish in plants: not only when the difference is between species, as in *Fragaria* and *Nicotiana*, but also between genera. Under natural conditions the sperm nucleus of *Vicia sativa* may expel the egg nucleus of *Lens esculentum* and proceed by doubling of its chromosome number to develop a normal plant, with the alien cytoplasm of the maternal parent. Furthermore distant hybridisation which is so disastrous in animals is remarkably successful in plants. Crosses between genera are frequent. Crosses between subfamilies in mosses, grasses and crucifers give vigorous progeny. Hybrids between *Saccharum* and *Bambusa* are fertile. Only that between *Saccharum* and *Zea* shows vegetative abnormality.[1]

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[1] Hadorn, 1937.

[2] "Dauermodifikation." Jolloš, 1934.

It seems therefore that there is an important difference in the part played by the cytoplasm in plants and animals. In both it is the agent of nuclear activity and of differentiation. In both it consequently passes through a cycle of adjusted changes. But in animals this adjustment is more complex, more rigid and therefore more persistent. So persistent is it that we may ask ourselves whether it may never be autonomous. That is the question we are now prepared to discuss.

We know nothing of any visible bodies outside the nucleus determining differentiation of cells during development. But we know of one kind of body whose reproduction can be followed and shown to be responsible for the inheritance of important properties. This body is the plastid of plant cells. In many algae it is seen throughout life as a green chloroplast. In some diatoms the chloroplasts are present in a small and constant number in each cell and when the diatom divides they are evenly distributed. Their transmission is therefore as regular as that of the nucleus. In some species of *Spirogyra* the chloroplasts are few and constant, but in others they are numerous and variable. Their transmission then is necessarily less regular. In the higher plants likewise they are numerous and variable. Moreover there are special cells devoted to vegetative reproduction in which plastids that will later be large and green in the leaves are small and colourless and difficult to identify. Nevertheless it seems likely that plastids throughout these plants are self-propagating bodies not arising *de novo* out of the cytoplasm.[2] The evidence is experimental.

In hundreds of plant species genes are known which control the colour of the plastids. The albino type appears as a Mendelian recessive which usually dies. In a number of species, however, the cross white-by-green is entirely white and the cross green-by-white entirely green. The colour of the plastids is maternally inherited. Actually a purely white parent cannot be used, but it so happens that white tissue arises by mutation in very many plants and owing to the regular separation of layers in the development of the plant an arrangement comes about by which a glove of white tissue is growing over a hand of green tissue. The subepidermal layer of white tissue produces the germ cells, the green layers do the work. Such chimaeras of *Pelargonium zonale* can be bred as though they were white, and from this breeding Baur was able to conclude that the plastids were self-maintaining organs of inheritance.

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[1] Janaki-Ammal, 1938.

[2] Chittenden, 1927.

Plastid mutations from green to yellow or white occur once in 2000 *Oenothera* plants, wild species or crosses. They appear as pale flecks or if they come early enough they develop into layers of pale tissue. Evidently the plastids maintain themselves, but also, unlike the genes, they are liable to sort themselves out at a mitotic cell division, so that purely white and purely green cells arise from mixed cells. This sorting out takes place slowly in *Antirrhinum* and *Mirabilis*, more quickly in *Pelargonium* and *Oenothera*, where egg cells for example are never mixed.[1]

Another property in which species differ is in regard to the plastids being carried over by the pollen tube. In *Antirrhinum* and *Zea* they are inherited exclusively through the egg. In *Pelargonium* and *Oenothera* a few usually enter from the pollen. A flaked plant is then produced from the cross green-by-white. The reciprocal cross dies too young for us to see the flakes.

What then is the relationship of nucleus and plastid? It is clear in some cases that the nucleus controls the colour of the plastid. It is equally clear in other cases that the plastid is as autonomous and permanent as any gene. The answer to this question is provided by certain critical experiments with *Oenothera*.[2]

As we saw (Ch. xvi) *Oenothera muricata* produces two types of gametes, *curvans* and *rigens*. If we take only the *curvans* progeny we find that the following cross is different in opposite directions:

Hookeri ♀ × *muricata* ♂—^{h}*Hookeri.curvans*: yellow
muricata ♀ × *Hookeri* ♂—^{h}*Hookeri.curvans*: green.

This means that *Hookeri* plastids are yellow with the *H.c* nucleus although they are green with a pure *Hookeri* nucleus, and although *muricata* plastids are green with the *H.c* nucleus.

Now the yellow seedlings die, but a few *Hookeri* plastids have been brought into the green seedlings and some of them develop yellow flakes and layers. Yellow-over-green shoots should then

[1] Renner, 1934.

[2] Renner, 1936.

breed from their yellow subepidermal layers as though they had pure *Hookeri* plastids. When selfed these shoots gave two kinds of progeny:

(i) ^{h}*Hookeri*.*curvans*: all yellow.
(ii) ^{h}*Hookeri*.^{h}*Hookeri*: all green.

When back-crossed with *muricata* pollen all the progeny is of the first type; with *Hookeri* pollen, of the second type.

Thus *Hookeri* plastids which become yellow with the *H.c* nucleus become green again with the pure *Hookeri* nucleus, and indeed with certain other nuclei as various other crosses show.

Tests of this kind show that the behaviour of the plastids depends on their reaction with the nucleus and that both partners to this reaction are permanent and autonomous. Hence although most plastid mutations to white or yellow are incompetent in any nucleus with which they can be combined by crossing, we are bound to suppose that the plastids and the nuclei of each *Oenothera* species have become mutually adapted for chlorophyll production by mutation and selection on *both* sides.[1]

Knowing the special properties of extra-nuclear inheritance shown by the plastids, we are in a better position to test the evidence of other determinants outside the nucleus. We must not expect absolute constancy; we must allow for sorting out. We must not expect absolute matrilinear descent in plants; we must allow for contamination by the pollen.

Reciprocal crosses between many pairs of species in plants differ, for example in *Epilobium*, *Streptocarpus*[2] and *Geranium*. They differ, not in resembling the mother plant more closely, but in new and precise modifications. Reciprocal crosses between *Funaria mediterranea* and *F. hygrometrica*, for example, differ in sporocarp shape. By regeneration meiosis can be avoided and diploid gametophytes produced vegetatively. These again differ in leaf shape. They still differ if maintained vegetatively for 13 years. And further, if haploid gametophytes are back-crossed to the male parent eight times, so that the product has the nucleus of the male parent and the cytoplasm of its matrilinear ancestor, it still does not agree in form with its male parent.[3]

There is no excuse for doubting that such tests show the action of a permanent cytoplasmic determinant. Or, should we say, determinants? The answer depends on the nature of the crosses. In a particular difference between reciprocal crosses of individuals with a single gene difference within *Solanum Lycopersicum*, or with no gene difference at all within *Zea Mays*,[1] a specific cytoplasmic determinant may be assumed. The same is true in *Linum usitatissimum*. A special gene from the tall flax aborts the anthers in a quarter of the F_2 progeny of its cross with the procumbent variety when this variety is used as the female parent. The same principle applies with the same result when the tall *L. angustifolium* and the procumbent *L. floccosum* are crossed. An homologous gene mutation has been accompanied by an homologous cytoplasmic change.[2] But where generalised or multiple effects are concerned a number of different determinants must be supposed to take part. Thus in *Vicia Faba* a number of plasmatic differences are to be inferred from reciprocal crosses between the subspecies *major* and *minor*. Amongst other effects the *minor* cytoplasm seems to eliminate the F_2 segregates which are pure for certain genes from the stock. There are six genes concerned and they are linked.[3] When we recall the importance of linkage groups in developing the discontinuity between species it begins to appear that this action on linked genes is not a coincidence but a consequence of special adaptation of the cytoplasm to the nucleus during the differentiation of the two races. It implies the existence of a number of different and specific determinants in the cytoplasm.

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[1] Renner, 1934.

[2] Oehlkers, 1938.

[3] Wettstein, 1937.

The variety of changes in plasma types similarly argues a specificity in these changes. In *Epilobium hirsutum* half a dozen stocks from different localities differ in their plasmatic properties, as shown in reciprocal crosses with one another and with *E. luteum*. They differ not only quantitatively but qualitatively and give in the extreme cases a variety of probably unrelated effects.[4]

The cross *luteum-hirsutum* has been back-crossed to the male parent thirteen times so as to give a *hirsutum* nucleus in an approximately *luteum* cytoplasm. This product may be represented as Lh^n. We then find that $Lh^{14} \times$ *luteum* resembles *luteum* × *hirsutum* and not the reciprocal cross. For example, it is male sterile. The cytoplasm of Lh^{14} remains after fourteen generations essentially *luteum*.

This is not the whole story. When a white-over-green *hirsutum* is used as the male parent of Lh^{14} one in 400 plants shows white flecks owing to the sorting out of pollen plastids from egg plastids.

[1] Rhoades, 1933. [2] Gajewski, 1937. [3] Sirks, 1931. [4] Michaelis, 1937.

Examination of this generation shows that about one in 400 also has shoots with fertile anthers. Further, the male-fertile flowers selfed give fewer sterile progeny than the male-sterile flowers of the same plant (using presumably the pollen of the fertile flowers). The plasmatic determinants therefore just as much as the plastids are sorted out in development. In fact plasmatic inheritance, like Mendelian inheritance, is particulate.

Particulate inheritance of the plasma does not mean that a single type of particle distinguishes *luteum* from *hirsutum*. As we saw, the several effects in *Vicia* and the several races in *Epilobium* indicate several kinds of particle. This is brought home to us in a special way by the same mutating plants of *Lh*^{14}. When the fertile flowers of *Lh*^{14} are crossed with *luteum* pollen they give less fertile progeny than do the sterile flowers in the same cross. The sorting out of a determinant affecting the fertility of pure *hirsutum* nuclear type does not mean the sorting out of a determinant affecting the fertility of a *hirsutum-luteum* hybrid. Different and independently assorting determinants are at work.[1]

Taking all these experiments together we see that genotype must be supposed to embrace three elements, nucleus, plastids and cytoplasm. All of these are subject to particulate inheritance and particulate variation. The nucleus in addition is subject to a super-particulate chromosome variation to which the others presumably are not. The particles in the nucleus are genes; those in the plastids and cytoplasm may perhaps be treated more rigorously if we also think of them as genes—plastogenes and plasmagenes. The fact that their specific properties can only be discovered in relation to the specific properties of nuclear genes in no way robs them of their specificity.

In order that we should find out something more about these free genes we must try to form a more precise picture of how they live, move and multiply. It seems likely that they are protein molecules or aggregates. Evidently they are such that, like true genes, they can arise only from proteins of the same kind—apart from mutation. Unlike true genes however their reproduction is not controlled by a *mechanical* equilibrium but will be subject rather to conditions of *chemical* equilibrium genotypically controlled but specific for each type of gene. The conditions of cytoplasmic heredity are therefore likely to show a wide variation according to the type of equilibrium to which the plasmagenes concerned are

[1] Michaelis, 1935.

subject. Probably also the high differentiation of animal cells is less likely to favour the survival of plasmagenes than the lower differentiation of plants.

The possible nature of the plasmagene is indicated by what we know of virus diseases. The virus is a protein molecule which, introduced into one organism, disappears; into another, multiplies to give a neutral equilibrium; into yet another, multiplies without limit and has deleterious or fatal results. If we look upon the virus as a protein taken out of one organism (usually by a parasite) and injected into another to which it is not properly adapted, we see that it has the properties often shown by a plasmagene in crosses between species. This is to suppose that a virus is not a primitive enemy of nature but just a protein out of place. Such is the position of the cytoplasm of one species which harbours the nucleus of another, and the varying behaviour of the one indicates the varying possibilities of the other.[1]

There are a large number of anomalous types of heredity which have hitherto failed to agree either with the requirements of segregation implied by nuclear determination or with the properties of matrilinear inheritance which were supposed to be implied by cytoplasmic determination. Laciniation in *Malva parviflora*,[2] rogues in *Pisum* and *Solanum Lycopersicum*, patterns in *Tagetes* and *Dahlia*, all provide examples of the less stable plasmagene equilibria which might be expected from variations within a species which have not become adapted to isolated and discontinuous genotypes.

The conditions of cytoplasmic inheritance indicate in these ways not only co-adaptation of the types of nuclear gene and plasmagene but also some degree of genotypic control in regard to the conditions of reproduction and equilibrium of the plasmagene. This control is limited by the molecular possibilities of the situation as it is in regard to the nucleus itself. How it is limited is a question which is likely to be answered in part by the study of virus reproduction. The very existence of plasmagenes however warns us of this molecular limitation to the adaptability of the genetic system. Plasmatic inheritance is not a help but a hindrance to adaptation. It is in itself clonal, and irregularly clonal at that. It is the first and the last contradiction to all the rules which have governed the evolution of genetic systems.

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[1] Cf. Salaman *et al.* 1938.

[2] Lilienfeld, 1929.

CHAPTER XXI

THE EVOLUTION OF HEREDITY

THE kinds of reproduction already set out show that there is not one system of heredity and variation but many. And these make the complete revolution from asexuality to sexuality and back again. Since the properties of heredity and variation themselves show heredity and variation under experiment they must, like other properties of the organism, be susceptible of selection and adaptation. The question now arises as to how far the present variation in genetic systems can show us the steps in their past evolution. This method has proved of value in comparative morphology and biochemistry. In comparative genetics we have even more to expect from it because the steps are fewer and many of them are still susceptible of the combined tests of experiments with cells and with organisms. Let no one imagine that the definition of these steps is a work of supererogation, a mere catalogue of superfluous conjectures, for no one can undertake a serious study of genetics without being compelled to make one or other of the alternative series of assumptions that are implied by the evolution of genetic systems—whether he knows that he is making these assumptions or not.

In the first place, the properties of heredity and mutation are common to all organisms from the virus to the many-celled animal or plant. We may therefore suppose, without grave risk, that the whole of evolution has a common origin and falls into genetic series which can be traced to this origin (Fig. 26).

The naked gene that we see in the virus is the prototype in reproduction and mutation of the three kinds of self-propagating molecule that we see to-day in the chromosomes, the plastids, and the plasmagenes of higher organisms. The plasmagene is a relic of the naked gene of pre-chromosomian times, a relic which is preserved in spite of its being a nuisance in heredity because it is a necessary cog in the machinery of development.

There are three important levels of organisation within this series. The lowest has no differentiation between genes. The second has a differentiation of genes but no sexual reproduction. The third has sexual reproduction with an alternation of haploid and diploid phases. Two important inventions made these changes of level possible. The first step was the differentiation of the genes which are still undifferentiated in viruses and bacteria. It is made possible by the invention of mitosis and the arrangement of the genes on linear threads. This means, as we have seen, that a chemical equilibrium was superseded by a mechanical one.

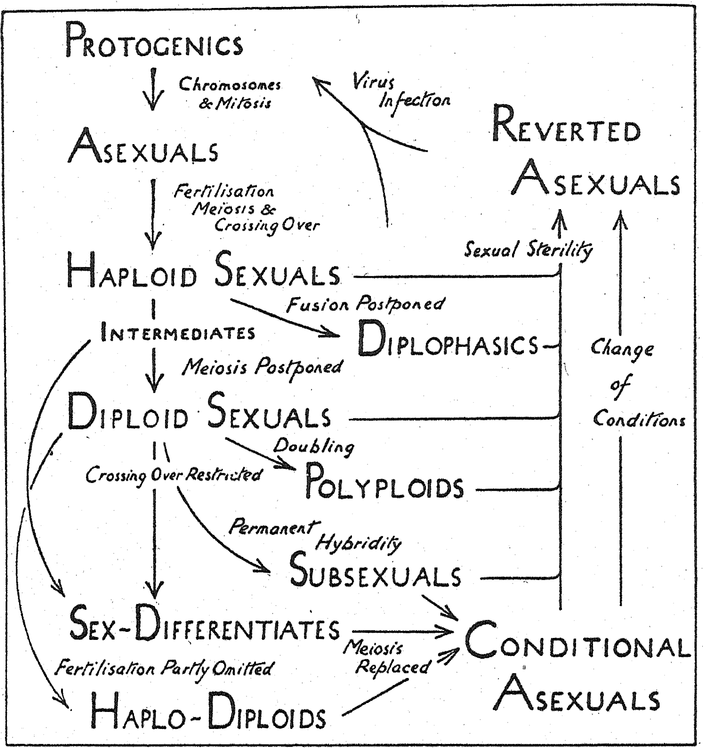
PROTOGENICS
Chromosomes & Mitosis
Virus Infection
REVERTED ASEXUALS
ASEXUALS
Fertilisation Meiosis & Crossing Over
Sexual Sterility
HAPLOID SEXUALS
Fusion Postponed
INTERMEDIATES
DIPLOPHASICS
Change of Conditions
Meiosis Postponed
DIPLOID SEXUALS
Doubling
Crossing Over Restricted
POLYPLOIDS
Permanent Hybridity
SUBSEXUALS
SEX-DIFFERENTIATES
Meiosis Replaced
CONDITIONAL ASEXUALS
Fertilisation Partly Omitted
HAPLO-DIPLOIDS

Fig. 26. Scheme representing the main steps concerned in the evolution of genetic systems.

Whether the asexual group of *Protista* can be supposed to correspond to these original mitotic organisms is doubtful. They may have reverted from sexual types. Likewise the Cyanophyceae indicate, by the apparent absence of mitosis, a degeneration of the genetic system. The original mitotic stage of evolution may therefore have disappeared. In the same way, as we saw, the virus may well be a reversion to the protogenic stage, the original naked genes having died out.

The second step was the adoption of sexual reproduction. It depended on the invention of meiosis as a modification of mitosis. The fusion of cells and nuclei is such a commonplace accident wherever mitosis occurs that the introduction of fertilisation involves no novelty. Meiosis on the other hand is an abrupt and revolutionary change which permits of no half-way house. The chromosomes must either reduce or fail to reduce if they are to keep their genetic character. Anything intermediate upsets the whole apple-cart. Likewise organisms, cells, and nuclei either copulate or they do not. The origin of meiosis and sexual reproduction therefore shows the most violent discontinuity in the whole of evolution. It demands not merely a sudden change but a revolution. It is impossible to imagine it as the result of a gradual accumulation of changes each one of which had a value as an adaptation either Lamarckian or Darwinian. If the material processes underlying sexual reproduction had been understood at the time neither Lamarck nor Darwin could ever have thought of evolution as depending on the adaptive accumulation of entirely continuous variations.

In all sexual species of organisms, so far as we know, from *Amoeba* to man, meiosis shows an extraordinary uniformity. It follows a standard course consisting of two divisions and demanding crossing-over between paired chromosomes as a condition of this segregation.

There is one other course that meiosis could conceivably have followed and that is in fact a simpler one. If chromosomes entirely failed to divide in the first division they would pair and separate very much as they do in meiosis in the male *Drosophila*. There seems no mechanical difficulty about such a system and it may indeed be found to occur some time in one sex in an animal. The reason why it has not provided the basis of sexual reproduction is clear. It does not allow of crossing-over, which depends on the division of threads while they are paired and coiled. And without crossing-over recombination is limited to whole chromosomes. Without crossing-over indeed sexual reproduction is meaningless.

The original change to meiosis would be one affecting all nuclear divisions in the cycle. We have to remember that a special timing of the action of a gene is an adaptation which can hardly be there before the gene itself has arisen by mutation. The precocity gene causing meiosis would therefore act as soon as a diploid nucleus had been formed. The haploid nucleus would have its precocious prophase which would not however upset mitosis since its chromosomes could not pair. The original sexual cycle is therefore one without any phase of diploid mitosis. Comparative morphology reaches the same conclusion. The simplest sexual organisms are those with meiosis immediately determined by the fusion of nuclei.

Two ways are then open to make a diploid phase possible. The first is the postponement of fusion found in the higher fungi. This curious method has been retained because, as Buller has shown, it permits the fertilisation of one fully developed mycelium by another. Like so many other genetic devices it reduces the cost of reproduction.

The second way is the postponement of meiosis by a differentiation in development between mitotic and meiotic divisions. This change prepared the way for the origin of all the higher plants and animals. In all of them it led to the gradual development of the diploid phase at the expense of the haploid one. Only once in evolution has the process been reversed. In the development of haploid testes by the diploid hermaphrodite *Icerya* meiosis has been pushed back in development.

In the regulation of diploid and haploid phases the simplest organisms show some elasticity, the higher organisms on the other hand an extreme conservatism. In the higher plants it is therefore possible to trace the ancestry of groups on this basis.

Let us now consider the principles shown by some of these evolutionary changes. In the first place what is the reason for this evolutionary conservatism? The spores of a fern can be changed to spermatozoids by a single mutation.[1] But a co-ordination of male and female organ production is necessary. They can therefore be changed only by the association of mutations. Hence the gradual change that has taken place must have been by slight mutations each of which would make another more desirable.

The interlocking action of genes is shown in a different way by the development of a differential sexual effect in the autosomes where sex chromosomes are differentiated from them. This as we saw is due to gradual atrophy of the *Y* chromosome. This atrophy in turn is due to the failure of natural selection to eliminate deleterious changes in the *Y*. This failure is due to the suppression of crossing-over between the *X* and *Y* on which their original differentiation depends. Such long chains of compensating or interlocked changes may be regarded as typical of all evolution at the highest level. They are always slow because they are integrated in their effects at every stage.

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[1] Andersson-Kottö and Gairdner, 1936.

Such integrated effects arise, although to a less extent, in considering adaptations of form. Every new variation of importance throws the organism into a new environment. In fact we may say that it is not the environment which changes the genes so much as the genes which change the environment. In adaptation the genotype is usually dominant over the environment. Every gene change demands others to act in concert with it. The stabilisation of a new combination depends in turn on structural change in the chromosomes at the right time and place to act in suppressing crossing-over. Hence the part that structural hybridity plays in setting up major discontinuities of all kinds.

In a word the unit of variation is not the unit of selection. Changes in the chromosome are determined by conditions of molecular stability. They are biologically at random. The combinations of these changes together with the selection of environments is what takes us from the chemical level of mutation to the biological level of adaptation.

It is a third corollary of integration that genetic systems can change while external forms remain the same. This is shown by the evolution of sex chromosomes but it can also be shown in other ways. Chromosomes can determine evolutionary discontinuities which are not morphologically visible. Two geographically separated varieties of *Hordeum sativum* give a vast array of segregation in their progeny which is not seen when parents with similar differences come from the same region.[1] The same kinds of gene difference in two species of *Gossypium* have different properties of dominance.[2] Certain *cryptic species* of *Drosophila* although scarcely distinguishable in form have chromosomes differently arranged and are inter-sterile.[3] All these properties go to show that the genetic basis of form may change although the form

[1] Karpechenko, 1935.

[2] Harland, 1936.

[3] Darlington, 1939.

itself does not. We need not suppose that the external stability of a *Lingula* depends on an unchanging complement of genes. The genes must change. Forms and their determinants are not necessarily related in the same way in different species at the same time, or in the same species at different times.

A fourth corollary of integration in the genetic system is compromise. Integration means that all the components of the genetic system are related to more than one function, all the functions to more than one component. The requirements of the different functions of the same component always differ. They may even be opposed. Hence selection enforces a compromise. The effective advantages are always the immediate ones. The compromises are often therefore short-sighted and short-lived.

The most fundamental compromise is that between high and low crossing-over. High crossing-over is demanded for the pairing of chromosomes, low crossing-over for the preservation of combinations. Another and related compromise is that between the requirements of hybridity, fertility and stability, a compromise which is resolved in entirely different ways in different species. A third compromise is that between true diploidy, which gives a sensitive balance, and polyploidy, which buffers the organism against unbalance and mutation. The vastly different ways in which these compromises are reached imply the imperfectibility of genetic systems.

And the last consequence of integration is that we meet the environment in three different relationships. For the cell in development, as we saw, the environment expresses itself through the intermediacy of the cytoplasm. It is an internal environment. For the individual in heredity the environment is external and is said to determine the total form of the individual in reaction with its genotype. For the genetic system in adaptation and evolution the environment consists of little else beyond the rest of the species. All its changes are, or can be, entirely neutral with regard to other parts of the external world. In all these relationships—development, heredity, and adaptation—we therefore see that the effective environment is itself dynamically subordinate to the genotype.

Thus the genetic system works at different levels of integration—the gene, the chromosome, the nucleus, the cell, and so on—and its activities at these different levels are interlocked in development and reproduction, in heredity and variation. Knowing something of this we can now consider afresh how selection works in more general terms.

The limits we can set to natural selection must depend on the limits we can set to heredity and variation. To Darwin, as to his predecessors, variation was undefined. It was a function of heredity; in his original theory it was no more than a principle of uncertainty inherent in heredity. The uncertainty might be negligible except in evolutionary time, as Johannsen's experiment showed, but it was universal. Omnia mutantur, nihil interit.

Our present knowledge still allows us to accept this statement as a first approximation. But we have to recognise that variations themselves continually interact and do so particularly through their effects on the genetic system. The uniformity he assumed in variation naturally implied to Darwin a uniformity in selection. He admitted only one special category—sexual selection. To us the great variety of genetic systems as well as the complexity we can see in any one of them means many types of variation and hence many types of selection. Let us see how these may be distinguished.

In the first place we realise that the great majority of variations that occur in nature are deleterious in themselves. The majority of them are lethal in the pure state. Now lethality is an expression of natural selection. It is not physiologically absolute. Lethal genotypes in *Drosophila* and *Oenothera* kill their bearers at any period before reproductive activity, and the time at which they take effect depends on external conditions. But from the point of view of natural selection lethality is absolute. With merely depressive mutations on the other hand it is a question of competition or a struggle for existence. This struggle obviously takes the form of a struggle for combination. New variations may have a deleterious effect in the combination and in the environment in which they originally occur. Carried through a population in a recessive condition they can appear in a more suitable environment and a more suitable combination where they can increase. This kind of variation although originally deleterious in the individual is advantageous to the species, since it renders it more adaptable to new environments. Absolute and competitive selection therefore play an entirely different part. The effect of the one is independent of the genetic system. It is purely conservative. The effect of the

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other, on the contrary, is constructive. And its effect depends almost entirely on sexual combination.

The classical theory of selection regarded the whole life cycle as a unit. Now we are able to realise the special implications of haploid selection. In plants the haploid generation is selected as such. The possibilities of adaptation of the diploid generation are therefore limited by the difficulty of restricting the action of every gene with precision to one time in the life cycle. They are also limited by the necessity that it shall act satisfactorily in both haploid and diploid dosage. The absence of such selection in animals on the other hand means less elimination of gametes and therefore greater elimination of zygotes in the offspring of hybrids. Sterility therefore establishes genetic isolation more readily. The size of the endogamous group and hence its hybridity equilibrium are reduced. Species are more distinct and more numerous.

The selection of germ cells is partly conservative and partly constructive. The same is true of the selection of meristematic cells. Cells with deleterious changes (such as chromosome loss in a diploid) are eliminated. Cells with advantageous changes (such as chromosome loss in a trisomic) are favoured. Hence the advantage of the multicellular meristem of the flowering plants. It allows greater scope for selection and gives greater vegetative stability of satisfactory types. This is important for largely vegetative species. It is a matter of life and death for strictly clonal species.

There is also a gene struggle as well as a cell struggle. Crossing-over is probably less frequent immediately adjoining the centromere than in other parts of the chromosome. Genes in this region, like those in the differential region of the *Y*, are therefore not capable of being freely recombined. Nor can they be freely selected. Their mutations will therefore be largely disadvantageous. If they become inert and immutable the efficiency of the genetic system as a whole will be increased. Hence the differentiation we find between parts of the chromosome in regard to activity and inertness, a differentiation which will itself necessarily stabilise the crossing-over system that gave rise to it. Thus gene mutability comes indirectly to promote stability at different levels of behaviour.

Selection therefore acts on the genetic system at every level, gene or chromosome, cell and individual, and in every stage and process, haploid and diploid, mitotic and meiotic, embryonic and adult. How is it related in time to the variations it acts on?

Lamarck, holding that hereditary variations were adaptive because they arose as a direct response to a changed environment, was bound to consider that they profited the generation which bore them. Darwin was surprised to discover that the sex ratio in animals seemed to be adapted to the needs of reproduction, that is, to the advantage of the following unborn generation.[1] He found this as much beyond the possibility of natural selection as it was evidently beyond the possibility of Lamarckian adaptation. He considered that "an individual with a tendency to produce more males than females would not succeed better in the battle for life than an individual with an opposite tendency; and therefore a tendency of this kind could not be gained through natural selection". It should be noted that a slightly different principle is involved in the assumption that neuter ants and bees can be selected, but it is one which is equally cogent evidence against Lamarckian inheritance. Darwin accepted this assumption and its anti-Lamarckian implications, although he did not accept the other. He was therefore confused by precisely the problem that now confronts us, the problem of selection acting at two levels of integration—the individual and the race. He concluded "that the problem is so intricate that it is safer to leave its solution for the future". In the light of our present knowledge of heredity the solution is clear. Properties of sex determination as well as of all other kinds of heredity are genotypically controlled; that is to say they are inherited, and are therefore capable of being selected for an indefinite number of generations after their origin. And, above all, they need not be selected or selectable in the generation in which they first arose.

Our understanding of the whole evolution of genetic systems depends in fact on the assumption that variations may survive merely because they favour posterity. The capacity for sexual reproduction could have conferred no advantage on the generation which first enjoyed it. No improvement in meiosis can benefit the individual in which it first arises. The elaborate genetic processes of self-sterility and the endless devices securing cross-pollination can yield no reward except in the qualities of the progeny. All these changes anticipate not merely the act of selection but the generation in which selection occurs. They all of them therefore put out of court any assumption of direct adaptation or the inheritance of acquired characters.[1]

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[1] Darwin, 1874; cf. Fisher, 1930; Crew, 1937.

This principle of *anticipation* in the evolution of genetic systems is of indefinite extension, and it is on this account that they show from time to time such contradictory vagaries. Sexual reproduction survives because it profits all posterity. The opposite state of apomixis survives because it profits its own immediate progeny. Permanent hybridity, subsexuality, and even polyploidy are changes made with immediate advantage at the expense of ultimate survival.

The combination of lag in the adaptation of the whole organism with anticipation in the change of its individual genes is responsible for another principle, namely that form overlaps function at both ends of the evolutionary as well as of the developmental time scale. Thus forms usually arise before they have a use; they always survive beyond their use. The principle of lag alone implies at once the instability of the compromises underlying adaptation, the irreversible character of evolution, the imperfectibility of its products, and the impossibility of stopping them from changing. The principle of anticipation alone proves that no adaptation of the genetic system could ever have arisen as a response to the environment. This is clear enough in the invention of chlorophyll and haemoglobin. In the invention of sexual reproduction any other view defeats the intelligence. New properties do not arise because they have a use, but having a use they survive.

Finally we see that integration and selection as shown by the genetic system are both related to one cardinal property: the recombination of genetic differences by sexual reproduction in systems maintained at a high level of hybridity. On general grounds we reach the same conclusion as on specific evidence: the development of the genetic system at the sexual stage depends on the pursuit of hybridity, a pursuit which is occasionally checkered by lapses into self-fertilisation and occasionally brought to a violent end by sterility and a return to asexual life.

The capacities of a genetic system for evolutionary change are limited by its properties at every level—by its cytoplasmic molecules, by its genes, their number, kinds, and stability, by its chromosomes and their properties of combination, by its mating system and sexual affinities, by the uniformity and stability both of its genotype and of its environment. Within these limits and at these levels, both severally and relatedly, natural selection controls the destiny of the system. We may say that the evolution of genetic systems is the history of the various ways in which these systems have come to expose their components to natural selection.

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[1] Darlington, 1932*b*.

The essential Darwinian principle of evolution by the natural selection of spontaneous and originally unadapted variation is upheld. But the different kinds of selection demanded by different kinds of heredity and variation and occurring at different levels of integration; the prolonged anticipation of selective changes with sexual reproduction and the lack of anticipation with asexual reproduction; the lag of adaptation demanded by discontinuity; and the imperfectibility of genetic systems demanded by this lag, an imperfectibility to which they are themselves adapted in their capacity for change—these are principles which can only now be deduced from considering how form, function and inheritance interact in every part of the organism and of the species, in space and in time.

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